FORMULATION AND CHARACTERIZATION OF IBUPROFEN SUSTAINED RELEASE TABLETS BY SOLID DISPERSION TECHNIQUE

A Dissertation submitted to
THE TAMIL NADU Dr. M.G.R. MEDICAL UNIVERSITY
CHENNAI - 600 032

In partial fulfillment of the requirements for the award of the Degree of
MASTER OF PHARMACY
IN
Branch - I: **PHARMACEUTICS**

Submitted by
MANJU.S
REGISTRATION No. 261611001

Under the guidance of
Mrs.C.RUBINA REICHAL, M.Pharm., (Ph.D).,
Associate Professor
Department of Pharmaceutics

CHERRAAN'S COLLEGE OF PHARMACY
COIMBATORE-641039
TAMILNADU.

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CHERRAAN'S COLLEGE OF PHARMACY

(Affiliated to the Tamilnadu Dr.M.G.R medical university, Chennai)

Approved by The Govt. of Tamilnadu, Chennai
All India Council for Technical Education, New Delhi
Recognized by pharmacy council of India, New Delhi

CERTIFICATE

This is to certify that the Dissertation entitled "**FORMULATION AND CHARACTERIZATION OF IBUPROFEN SUSTAINED RELEASE TABLETS BY SOLID DISPERSION TECHNIQUE"** submitted to The Tamilnadu Dr. M.G.R Medical University, Chennai, is a bonafide project work of **Reg No: 261611001** carried out in the department of Pharmaceutics, Cherraan's College of Pharmacy, Coimbatore for the partial fulfillment for the degree of Master of Pharmacy under my guidance during the academic year 2016-2018.

This work is original and has not been submitted earlier for the award of any other degree or diploma of this or any other university.

Place: Coimbatore

Date:

Mrs. C.Rubina Reichal, M.Pharm.,(Ph.D.)
Associate Professor,
Department of Pharmaceutics,
Cherraan's college of Pharmacy,
Coimbatore.

521. Siruvani Main Road, Telungupalayam, Piruvu, Coimbatore 641039
Phone: 2311066, 2346194, 2343380 Fax: 0422-2341066 E-Mail:cihs2002@Yahoo.Co.In

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Place: Coimbatore

Date:

Dr. P.Selvam, M.Pharm, Ph.D., FNABS., FISNS.,
Principal
Cherraan's College of Pharmacy,
Coimbatore.

521. Siruvani Main Road, Telungupalayam, Piruvu, Coimbatore 641039
Phone: 2311066, 2346194, 2343380 Fax: 0422-2341066 E-Mail:cihs2002@Yahoo.Co.In

EVALUATION CERTIFICATE

This is to certify that the dissertation work entitled **"FORMULATION AND CHARACTERIZATION OF IBUPROFEN SUSTAINED RELEASE TABLETS BY SOLID DISPERSION TECHNIQUE"** submitted by **Reg.No 261611001** to The Tamilnadu Dr. M.G.R medical university, Chennai, in the partial fulfillment for the degree of Master of Pharmacy in Pharmaceutics is a record of bonafide work carried out by the candidate at the Department of Pharmaceutics, Cherraan's College of Pharmacy, Coimbatore and was evaluated by us during the academic year 2016-2018.

INTERNAL EXAMINER **EXTERNAL EXAMINER**

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DECLARATION

The research work emboided in this work **"FORMULATION AND CHARACTERIZATION OF IBUPROFEN SUSTAINED RELEASE TABLETS BY SOLID DISPERSION TECHNIQUE"** was carried out by me in the department of Pharmaceutics, Cherraan's college of Pharmacy, Coimbatore under the direct supervision of **Mrs. C.Rubina Reichal, M.Pharm.,(Ph.D.),** Associate Professor Department of Pharmaceutics Cherraan's College of Pharmacy, Coimbatore-39.

The dissertation submitted to The Tamilnadu Dr. M.G.R Medical University, Chennai, for the award of degree of Master of Pharmacy in Pharmaceutics during the academic year of 2016-2018.

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S.MANJU

CONTENT

LIST OF TABLES

LIST OF FIGURES

ABBREVIATIONS

CDDS	-	Controlled Drug Delivery System
%	-	Percentage
Mg/ml	-	Microgram per millilitre
ºC	-	Degree celsius
Cms	-	Centimeter
DSC	-	Differential scanning calorimetry
e.g	-	Example
F	-	Formulation
FTIR	-	Fourier transform infrared spectroscopy
g/ml	-	gram per millilitre
GIT	-	Gastro intestinal tract
HPMC	-	Hydroxypropyl methylcellulose
hrs	-	Hours
ICH	-	International conference on harmonization
HR	-	Hasuner's Ratio
g/Cm^3	-	$gram/Centimeter^3$
IB	-	Ibuprofen
mg	-	milligram
ml	-	milliliter
nm	-	nanometer
PVP	-	Polyvinyl Pyrrolidine

RH	-	Relative Humidity
pH	-	Negative Log of Hydrogen Ion Concentration
S.R	-	Sustained Release
S.D	-	Standard Deviation/Solid Dispersion
UV	-	Ultra Violet
Θ	-	Angle of Repose
%.D.R	-	Percentage of Drug Release
% C.D.R	-	Cumulative Percentage of Drug Release
β	-	Beta
±	-	Plus or Minus
LBD	-	Loose Bulk Density
TBD	-	Tapped Bulk Density
SI.No.	-	Serial number
Vol	-	Volume
W/V	-	Weight per volume

INTRODUCTION

ORAL DRUG DELIVERY SYSTEM:

Over the past 30 years, as the expense and complications involved in marketing new drug entities have increased, with concomitant recognition of the therapeutic advantage of controlled release drug-delivery, greater attention has been focused on development of sustained or controlled release drug delivery system. These are several reasons for the attractiveness of these dosage forms. It is generally recognized that for many disease states, a substantial number of therapeutically effective compounds already exist. The effectiveness of these drugs, are, is often limited by side effects or the necessity to administer the compound in a clinical setting. The goal in designing sustained or controlled delivery system is to reduce the frequency of dosing or to increase effectiveness of the drug by localization at the site of action, reducing the dose required or providing uniform drug delivery.[1,2]

1.1 CONTROLED RELEASE DRUG DELIVERY SYSTEM (CDDS)

The goal of any drug delivery system is to provide a therapeutic amount of drug to the proper site in the body to achieve promptly and then maintain the desired drug concentration. The drug-delivery system should deliver drug at a rate dictated by the needs of the body over a specified period of treatment. A number of systems containing hydrophobic and waxes were fabricated with drugs in to dosage forms with the aim of sustaining drug levels and hence drug action for an extended period of time.[3]

Terminology

Modified release delivery systems may be divided conveniently in to four categories

1. Delayed release
2. Sustained release
3. Site-specific targeting
4. Receptor targeting

Delayed release

Delayed release systems are those that use repetitive, intermittent dosing of a drug from one or more immediate-release units incorporated in to a single dosage form. Examples of delayed release systems include repeat action tablets and capsules and enteric coated tablets where timed release is achieved by barrier coating.[4]

Sustained release

Sustained release systems include any drug delivery system that achieves low release of drug over an extended period of time sustained drug action at a determined rate by maintaining a relatively constant, effective drug level in the body with concomitant minimization of undesirable side effects.

Site specific targeting

In site specific targeting, the target is adjacent to or in the diseased organ or tissue.

Receptor targeting

In receptor targeting, the target is the particular receptor for a drug within a organ or tissue.

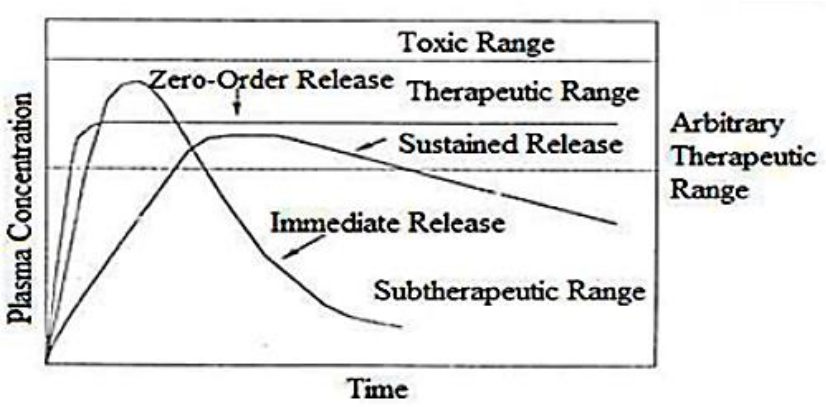


Figure 1: Plasma drug concentration profiles for conventional tablet formulation, a sustained release formulation and a zero order controlled release formulation.

1.2 SUSTAINED RELEASE FORMULATIONS

The concept of sustained release formulation was developed to eliminate the need for multiple dosage regimens, particularly for those during requiring reasonably constant blood levels over a long period of time. In addition, also has been adopted for those drugs that need to be administered in high dose, but where too rapid drug release is likely to cause undesirable side effects.[6]

Formulation methods used to obtain the desired drug availability rate in sustained action dosage forms include

1. Increasing the particle size of the drug
2. Embedding the drug in a matrix
3. Coating the drug or dosage form containing the drug
4. Forming complexes of the drug with materials such as ion exchange resins.

Advantages of sustained release drug delivery system

- **Improved** patient **convenience and compliance** due to less frequent drug administration
- Reduction in fluctuation in steady- state level and therefore **better control of disease condition.**
- **Increased safety margin** of high potency drug due to better control of plasma levels.
- **Maximum utilization of drug** enabling reduction in total amount of dose administered.
- **Reduction in health care cost** through improved therapy, shorter treatment period.
- Less frequency of dosing and reduction in personnel time to dispense, administer monitor patients.
- Better control of drug absorption can be obtained, since the high blood level peak that may be observed after administration of a dose of high availability drug can be reduced.

Disadvantages of sustained release drug delivery system

- **Decreased systemic availability** in comparison to immediate release conventional dosage form. This may be due to
  - Incomplete release
  - Increased first-pass metabolism, increased instability
  - Site specific absorption, pH dependent solubility, etc.
- Poor ***in vitro-in vivo*** correlation.
- Possibility of dose dumping.
- **Retrieval of drug is difficult** in case of toxicity, poisoning, or hypersensitivity reactions.

- Higher cost of formulation.
- The physician has **less flexibility** in adjusting dosage regimens. This is fixed by the dosage form design.

Rationale for sustained release:

- Drugs which are often administered repeatedly at specified time interval to maintain therapeutic level in blood or blood tissues.
- Uniform drug response achieved by using different combination of doses and dosage interval.
- However, the dosage regimen of an orally administered drug may be considered to be optimal when the therapeutic effect is maintained for the desired duration of the treatment at the lowest frequency of administration.
- Frequent administration of dose produces side effect.

1.3 PHYSICOCHEMICAL FACTORS INFLUENCING ORAL SUSTAINED RELEASE DOSAGE FORM DESIGNING

The performance of a drug in its release pattern from the dosage form as well as in the body proper is a function of its properties. Most of the time this properties are restrictive rather than prohibitive, making sustained/convenient to describe the physiochemical properties of the drug.[6]

Dose size

For orally administered systems, there is and upper limit to the bulk size of the dose to be administered. In general, a single dose of 0.5 – 1 g is considered maximal for a convenient dosage form. This also holds for sustained release dosage forms. Those compounds that require a large dosing size can sometimes be given in multiple amounts or formulated in to liquid systems. Another consideration is the margin of safety involved in administration of large amount of a drug with a narrow therapeutic range.

Aqueous solubility

Since drugs must be in solution before they can be absorbed. Compounds with very low aqueous solubility usually suffer oral bioavailability problems because of limited gastrointestinal transit time of the undisclosed drug particles and limited solubility at the absorption site. Unfortunately, for many compounds, the site of maximum absorption will also be the area in with the drug is least soluble. The choice of mechanism for oral sustained/controlled release system is limited by aqueous solubility of the drug. Diffusion, systems will be poor choices for slightly soluble drugs since the driving force for diffusion, the incorporated in matrix systems. In selecting polymer coatings for sustained/controlled system, the dissolution rate of a drug must be considered. Some antibiotics and high molecular weight drugs may have reasonable well to excellent aqueous solubility, but very slow dissolution rates. On the positive side, the slow dissolution rate of such compounds can be utilized to achieve sustained/controlled drug release by incorporation in a matrix system.

Partition coefficient and molecular size

Partition coefficient and molecular size influence not only the permeation of a drug across the biological membranes, but also diffusion across or through a rate-controlling membrane or matrix. Drugs with extremely high partition coefficient (i.e., very oil-soluble) readily penetrate the membranes but unable to proceed further, while drugs with excessive aqueous solubility, i.e., low oil/water partition coefficients cannot penetrates the membranes. A balance in the partition coefficient is needed to give an optimum flux for permeation through the biological rate controlling members.

Drug stability

Drugs that are unstable in the stomach can be placed in a slowly soluble form or have their release delayed until they reach the small intestine. To achieve better bioavailability and controlled release of drugs that are unstable in the small intestine, a different route of administration should be chosen. Controlled release of nitro-glycerine is a good example. On the positive side, the presence of metabolizing enzymes at the site of administration or along the pathway to the target area can sometimes be utilized in controlled drug delivery.

1.3 BIOLOGICAL FACTORS INFLUENCING ORAL SUSTAINED RELEASE DOSAGE FORM DESIGN

The design of a sustained/controlled release product should be based on a comprehensive picture of drug disposition. This would entail a complete examination of the ADME characteristics of a drug following multiple dosing. Every pharmacokinetic property and biological response parameter has a useful range for the design of sustained/controlled release products.[12]

Biological half-life

The usual goal of an oral sustained release product is to maintain therapeutic blood levels over an extended period. To achieve this, drug must enter the circulation at approximately the same rate at which it is eliminated. The elimination rate is quantitatively described by the half-life($t_{1/2}$). Each drug has its own characteristic elimination rate, which is the sum of all elimination process, including metabolism, urinary excretion, and all other processes that permanently remove drug from the blood stream.

Therapeutic compounds with short half-lives are excellent for sustained release preparations, since this can reduce dosing frequency. However, this is limited, in that drugs with very short half-lives may require excessively large

amount of drug in each dosage unit to maintain sustained effect; forcing the dosage form itself to become limiting large. Compounds with long half-lives more than 8 hours are also generally not used in sustained forms, since their effect is already sustained.

Absorption

To maintain constant blood or tissue level of drug. It must be uniformly released from the controlled release system and then uniformly absorbed. Usually, the rate-limiting step in drug delivery from a controlled release product is release from the dosage form rather than absorption. The drugs absorption by specialized transport processes and drugs at special sites of the GI tract are also poor for controlled release products. To formulate drugs at the lower limit of absorption rate constants in to controlled or sustained release systems, the desired rate constants of release systems, the desired rate constants of release from the dosage form would have to be even lower, resulting in decrease bioavailability. As the GI transit time is finite, a suitable controlled release system, giving a high fraction of dose absorbed, can be difficult to design. In addition, the rate constant of release based on absorption consideration may be very different from that based on biological half-life considerations so that a compromise is achieved generating less than ideal release rates. In essence, oral drugs which are slowly absorbed are poor for sustained dosage forms primarily because drug availability is limiting by GI transit time.

Distribution

The distribution of drugs into tissues can be an important factor in the overall drug elimination kinetics since it not only lowers the concentration of circulating drug but it also can be rate limiting in its equilibration with blood and extra cellular fluid. In the bound portion of a drug can be considered inactive and unable to cross membranes.

At high binding one sees prolonged drug action. The apparent volume of including binding, within the body. Conceptually, this pharmacokinetic parameter can be viewed as a proportionality constant relating plasma or serum concentration of drug to total amount of drug in the body. Consequently, the apparent volume of distribution assumes different values depending on the time course of drug disposition. The apparent volume of distribution influences the concentration and amount of drug either circulating in the blood or in target tissues. It can also influence the elimination kinetics of a drug.

The total apparent volume of distribution for a drug at steady state can be calculated by

$$\mathbf{V_dS_s=[(K_{12}+K_{21})/K_{21}]V_p}$$

Where,

V_dS_s is apparent volume of distribution at steady state.

K_{12} is the constant for distribution of drug form the central to peripheral compartment.

K_{12} is that from the peripheral to control compartment.

V_p is the volume of the central compartment.

Metabolism

Metabolism of a drug can either inactivate an active drug or convert an inactive drug to an active drug to an active metabolite. Metabolic alteration of a drug can occur in a variety of tissues, some of which are richer in enzymes than others. For example, the organ most responsible for metabolism is the liver and thus the greatest metabolic conversion occurs after a drug has been absorbed in to the general circulation. Metabolism of a drug will be reflected in the elimination constant of a drug or by the appearance of metabolite. There are two areas concern relative to metabolism that significantly restrict sustained release product design.

$$\mathbf{J= (1/A)dm/dt}$$

If the concentration gradient is liner and the thickness of the diffusion layer is h,

dc/dx=(Cb-Cs)/h

where Cs is the concentration at the solid surface and Cb is the concentration in the bulk solution. By combining the above equation, the flow rate of material is given by

Dm/dt=-(DA/h)(Cb-cs)= kA(Ca-cb)

Where k is the intrinsic dissolution rate constant.

The above equation predicts constant dissolution rate if the surface area, diffusion coefficient, diffusion layer thickness, and concentration differences are kept constant.

Most of the products fall into two categories

- Encapsulation dissolution control
- Matrix dissolution control

Encapsulation dissolution control

These methods generally involve coating individual particles or granules of drug with a slowly dissolving material. The coated particles can be compressed directly into tablets as in space tabs or placed in capsules as in the spanule products.

Matrix dissolution control

The reduced drug solubility plus larger particle size can be used to modify available rates. There is an upper restriction on the size of particles one can employ for the oralzoute while the low solubility approach will produce a changing dissolution are as the area for dissolution decrease. An alternate

approach is to compress the drug with a slowly dissolving carrier of some sort in to a tablet form. Here, the rate of drug availability is controlled by the rate of penetration of the dissolution fluid in to the matrix. This, in turn, can be controlled by porosity of the tablet matrix, the presence of hydrophobic additives, and the wettability of the tablet and particle surface. The porosity of the tablet, i.e., surface area available, can be altered in a compressed tablet by compression force, adhesion between adjacent particles as well as size and shape of the particles. In addition, hydroscopic fillers can be added to decrease the effective porosity be limiting the number of pores that can be penetrated by the eluting fluid.

A major disadvantage of matrix devices is that drug release rate continuously decreases with time. This is a consequence of increase diffusional distance and decreased surface area at the penetrating solvent front. Consequently to achieve zero order release from matrix devices is will be necessary to select a geometry that compensates the increase in diffusional distance with a corresponding increase in surface area for dissolution. In principal these systems can be used in oral controlled delivery where absorption at the specific site in the intestine is desired.[10]

1.5.2 Diffusion controlled release

There are basically two types of diffusion controlled systems which have been developed over the past two decades: reservoir devices and matrix device.

Reservoir devices

In this system, a water insoluble polymeric material encloses a core of drug .Drug will partition in to the membrane and exchange with the fluid surrounding the particle or tablet. Additional drug will enter the membrane. Diffuse to the periphery, and exchange with surrounding media.[11]

The flux of drug, J (in amount/area-time),across a membrane in the direction of decreasing concentration is given by ficks first law:

J=-D dC/dx

Where D is the diffusion coefficient in area/time and dc/dx is the change of concentration C with a distance X. Assuming steady state, above equation can be integrated to give:

J=-D C/1

In Terms of the amount of drug released, the release rate Dm/dt is given by

dM/dt=ADK.AC/1

Where,

A is the area,

D is the diffusion coefficient,

K is the partition coefficient of drug between the membrane and drug core,

I is the diffusional path length (thickness of coat in the ideal case), and

C is the concentration difference across the membrane.

As important parameter in above equation is the partition coefficient which is defined as the concentration of drug in membrane over all concentration drug in the core. If the partition coefficient is high. The core will depleted of drug in a short time so that zero order release will be observed only over short segment of the time course of drug release.[10]

Matrix devices

In this system, a solid drug is dispersed in an insoluble matrix. The rate of drug release is dependent on the rate of drug diffusion but not on the rate of solid dissolution. The appropriate equation describing drug release from this system has been derived by T.Higuchi.

Q= (D€/T(2A-€C,)C,t)1/2

Where,

Q=weight in grams of drug release per unit surface area

D=diffusion coefficient of drug in the release medium

€=porosity of the matrix

T=tortuosity of the matrix

Cs=solubility of drug in the release medium

A=concentration of drug in the tablet, expressed as g/m.

For purposes of date treatment the above equation is usually reduced to;

Q=Kt1/2

Therefore a plot of amount of drug released versus the square root of time should be linear if drug release from the matrix is diffusion controlled.

1.5.3. Diffusion and dissolution controlled systems:

The main feature is that the drug core is enclosed with a partially soluble membrane. Dissolution of part of the membrane allows for diffusion of the continued drug through pores is the polymer coat. The release profile of drug from this type of product can be described by the following equation:

Release rate = $AD(C_1-C_2)/1$

Where A, D and I are the surface area, diffusion coefficient of drug through pore, and diffusion path length, respectively. C1 as the concentration of drug in the core and C2 is that in the dissolution medium. The fraction of soluble polymer in the coat will be dominant factor controlling drug release.

1.5.4 Ion-exchange resins:

It is an attractive method for sustained drug delivery because, in theory, drug release characteristics rely only on the ionic environment of the resin containing the drug and should therefore be less susceptible to environmental conditions. Such as enzyme content and pH, at the site of absorption. Resins are water-insoluble materials containing anionic or cationic groups in repeating positions on the resin chain. When a high concentration of an appropriately charged ion is in contact with the ion-exchange group, the drug molecule is exchanged and diffuses out of the resin to the bulk solution according to the following scheme.

Resin $[M(CH_3{}^+Z$ Resin $[N(CG_3)]\ {}^+Z+X^-$

Or

Resin $(SO_3)A^+ + B^+$ resin $(SO_3)\ B^+ + A+$

Where X- and A+ are drug ions

Before the eluted Ion an diffuse out, the eluting ions must diffuse into the resin matrix and establish and establish equilibrium with the ionic resin group. As with all diffusion process, the area of diffusion and diffusional path length are important to the rate of diffusion, In addition, the amount of solvent in the matrix of the resin, as well as the structural rigidity of the resin, i.e. cross-linking, also influences the drug diffusion rate. For this reason, the porosity of the resin and the size of the bead of particle must be carefully controlled during the formulation process.[11]

1.5.5 RELEASE MECHANISM OF MATRIX SYSTEM:

Higuchi provided the theoretical basis for defining drug release from inert matrices. The equation describing drug release from the plannar surface – of an insoluble matrix is

DMt/dt= A [square root of(2DcsCo)]/A [square root of (t)]

Where, d Mt/dt = the rate of drug release form surface of the system,

A = surface area of system

D = drug diffusion coefficient through polymer,

Cs = drug solubility in polymer,

Co = total drug concentration in the matrix and it is the time.

Q = ([D€ Cg/T) [2A-C-Cs] t]1/2……..(1)

Where,

Q is the amount of drug release per unit surface after time t.

€ is the porosity of the matrix

D is the diffusion co-efficient

T is the tortuosity of the matrix

Cs is the solubility of the drug in the elution medium

A is the initial loading dose of drug in the matrix

Drug release is triggered by penetration of eluting media into the matrix dissolving the drug, thereby creating channels through which diffusion takes place. A

High tortuosity means that the effective average diffusion path is large. The porosity items takes in to account the space available for drug dissolution; an

increased porosity results in increased drug release. Both porosity and tortuosity are functions of the amount of dispersed drug, the physio chemical properties of the matrix, and the dispersion characteristics of the drug in the matrix.

If the drug is freely soluble in the elution medium that is Cs>>A, such that the dissolution rate is rapid, then equation(2), which describes the release of drug from a solution entrapped in an insoluble matrix applies:

$Q = 2A (Dt/IIT)^{1/2}$…….(2)

Release rate is directly proportional to the amount of dispersed drug A: it is proportional to $A^{1/2}$ for insoluble drugs if 2A = Cs. These expressions predict the plots of Q Vs. $t^{1/2}$ be linear. Release of water soluble drugs, however should be unaffected by the amount of liquid pH value, enzymes content and other physical properties of digestive fluids, unless the drug is in a salt from that precipitates within the matrix pores on dissolution when penetrated by acidic or basic media. Release kinetics.

To study the mechanism of drug release from matrix tablets, the release data were fitted to the following equation: Zero-order equation = Qo – kot (1)

Where Q is the amount of drug release at time t, and ko is the release rate;

First – order equation ; In Q = In Qo – k_1t(2)

Where K_1 is the release rate constant:

Higuchi' equation: $Q = K_2 t^{½}$ (3)

Where Q is the amount of drug release at time t, and k_2 is the diffusion rate constant.[12]

SOLID DISPERSION

The term solid dispersion refers to a group of solid products consisting of at least two components, generally a hydrophilic matrix and a hydrophobic drug.

The matrix can be either crystalline or amorphous. The drug can be dispersed molecularly, in amorphous particles or in crystalline particles.

Oral availability of drug depends on its solubility and/or dissolution rate, therefore major problems associated with these drugs was its very solubility in biological fluids, which results into poor bioavailability after oral administration. Many methods are available to improve dissolution rate, solubility characteristics, including salt formation, micronization and addition of solvent or surface active agents. The term solid dispersion refers to a group of solid products consisting of at least two components, generally a hydrophilic matrix and a hydrophobic drug. The matrix can be either crystalline or amorphous. The drug can be dispersed molecularly, in amorphous particles or in crystalline particles.

Solid dispersion is one of these methods, which was most widely and successfully applied to improve the solubility, dissolution rates and consequently the bioavailability of poorly soluble drugs. The concept of solid dispersions (SD_S) was introduced in 1961 by Sekiguchi and Obi, in which the drug is dispersed in inert water-soluble carrier at solid state. Several water soluble carriers such as hydroxyl propyl methyl cellulose, ethyl cellulose, beta cyclodextrin, urea, lactose, citric acid, poly vinyl pyrrolidone(PVP) and poly ethylene glycols such as carriers for Solid dispersion.[15]

Advantages of solid dispersion

- Particles with reduced particle size
- Particles with improved wettability
- Particles with higher porosity
- Drugs in amorphous state.

Disadvantages of solid dispersion

Though they increase the bio-availability of the drugs by increasing the solubility, their commercial use has been limited primarily because of

- Formulation development
- Solid state structure
- Mechanisms for dissolution enhancement are poorly understood in majority of cases.
- Manufacturing difficulties
- Stability problems
- Scale up.

CARRIERS USED AND THEIR CHARACTERISTICS:

The most commonly used hydrophilic carriers for solid dispersion includes

- Polymers like PVP, PEG, HPMC etc.,
- Lipids such as polyglycolized glycerides
- Surface active carriers
- Cyclodextrins.

CHARACTERISTICS:

- Hydrophilicity
- Physically and chemically inert
- Good solubility for drugs
- Compatibility with other ingredients of formulations
- Non toxicity.

FACTORS GOVERNING DRUG RELEASE FROM SOLID DISPERSION

1. Natural carrier

More hydrophilic nature of carriers enhances the faster release of drugs from solid dispersion. A poor water soluble or insoluble carriers may leads to slower release of drug.

2. pH dependent

As active drug incorporated into pH dependent polymers and was present dispersion state, the release of the drug from solid dispersion depends on the dissolution rate of the polymers which is mainly influenced by pH of the dissolution medium.

3. Effect of other excipients on drug release

The dissolution rate of the drug is increased when excipient like solubilising excipients are incorporated into the solid dispersion.

- When hydrophilic and lipophilic excipients where combined and incorporated, a remarkable enhancement of dissolution rate was observed.
- Incorporating self -micro emulsifying excipient also enhanced dissolution by forming dispersible particles with in the aqueous medium.
- Solid dispersion with no pharmaceutical excipient incorporated, enhanced the dissolution rate to certain extend only, It is only two fold compare to pure drug.[16]

PREPARATION OF SOLID DISPERSIONS:

Various preparation methods for solid dispersion are;

- Fusion method
- Solvent method
- Melting solvent method (melt evaporation)
- Melt extrusion method
- Lyophilisation Technique
- Melt Agglomeration Process
- The use of surfactant
- Super Critical Fluid (SCF) Technology

- Co-precipitation method
- Gel-entrapment method
- Kneading method

CHARACTERISATION OF SOLID DISPERSION

A. Detection of crystallinity in solid dispersions.

B. Detection of molecular structure in amorphous solid dispersions.

Currently, the following technique are available to detect (the degree of) crystallinity

1. Powder X-ray diffraction
2. Infrared spectroscopy (IR)
3. Water vapour sorption
4. Isothermal micro calorimetry
5. Dissolution calorimetry
6. Macroscopic techniques.

Alternative strategies:

A. Spraying on sugar beads using a fluidized bed coating system

B. Direct capsule filling

C. Electrostatic spinning method

D. Surface-active carriers.[17]

Enhancement of drug release from solid dispersions:

The increase in dissolution rate achieved by solid dispersion is by a combination of following effects,

- Reduction of particle size to such an extend can't be achieved by other conventional methods.
- By increasing the wettability of drugs as it is hydrophilic in nature.

- Reduced aggregation and agglomeration.
- By increasing its solubility in water due to hydrophilic nature of carrier.
- However, the main mechanism controlling the release of drug from the solid dispersions are not fully understood an proposed theories are depended on understanding of dissolution behavior of both the components of the dispersion.
- Recently, a method of measurement of viscosity of dissolution medium as the polymer dissolves from the solid dispersion as used to know the amount of drug release. This is Micro viscometry techniques(MVT).[20]

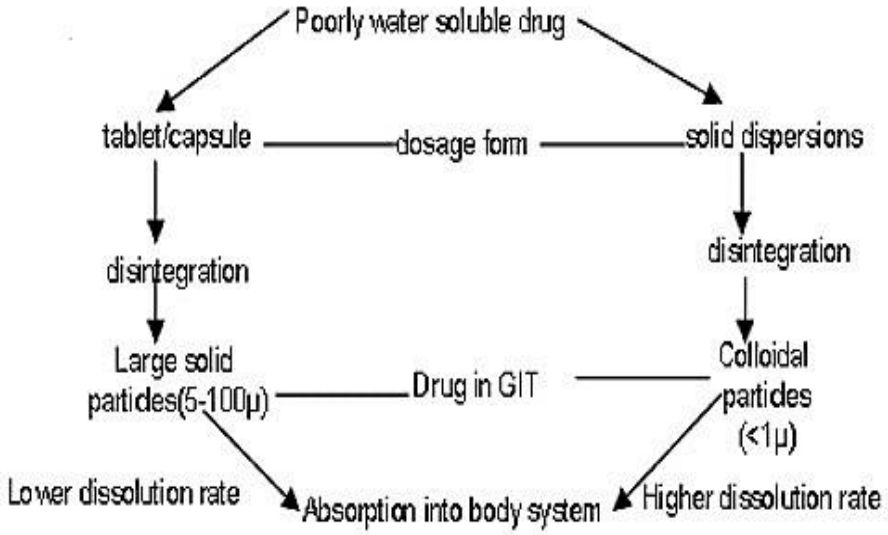


Figure 2: Schematic representation of the bioavailability enhancement of poorly water soluble drug by solid dispersion technique.

Methods to increase solubility:

By using the following methods solubility can be increased,

A. Kneading method
B. Precipitation method
C. Solid dispersion/ Co evaporated dispersion
D. Spray drying
E. Freeze drying
F. Melting
G. Neutralization method
H. Grinding

APPLICATION OF SOLID DISPERSION

- To increase the solubility, dissolution rate, absorption and bioavailability.
- Improved the stability.
- To reduce side effect of certain drugs.
- Masking of unpleasant taste and smell of drugs
- Improvement of drug release from ointment, tablets, creams.[13]

ARTHRITIS:

"Arthritis" literally means "inflamed joints". Arthritis primarily affects the joints; it also attacks muscles and connective tissues of the surrounding organs. Arthritic disease stems from injuries, defects in the immune system, wear a tear on the joints, infections or genetic predisposition.[21]

A. Osteoarthritis:

A degenerative joint disease and the most common of arthritis and joint disorders, is the gradual deterioration of cartilage, usually in the larger, weight bearing joints such as the hips, knees, and spine. This wear and tear is normal

process predominantly found in people of age 55 and older. It occurs more often in men. The joints are not always inflamed; the articular cartilage may begin to flake and crack, due to over use or injury. In severe cases the underlying bone becomes thickened and distorted. Scar tissue may then replace damaged cartilage. If movement becomes painful and restricted, lessened use of the associated muscles will lead to their atrophy.

B. Rheumatoid arthritis:

Rheumatoid arthritis is traditionally considered a chronic, inflammatory autoimmune disorder that causes the immune system to attack the joints. It is a disabling and painful inflammatory condition, which can lead to substantial loss of mobility due to pain and joint destruction. Rheumatoid arthritis is a systemic disease, often affecting extra articular tissues throughout the body including the skin, blood vessels, heart, lungs, and muscles.

The joint lining, called the synovium, becomes inflamed in case of rheumatoid arthritis, leading to pain, stiffness, warmth, redness and swelling. These inflamed cells release an enzyme that may even digest cartilage and bone.

A number of different pathological mechanisms are involved in rheumatoid arthritis. Lymphocytes have an important role and many inflammatory cells in the synovial sublining layer are lymphocytes, especially T cells.

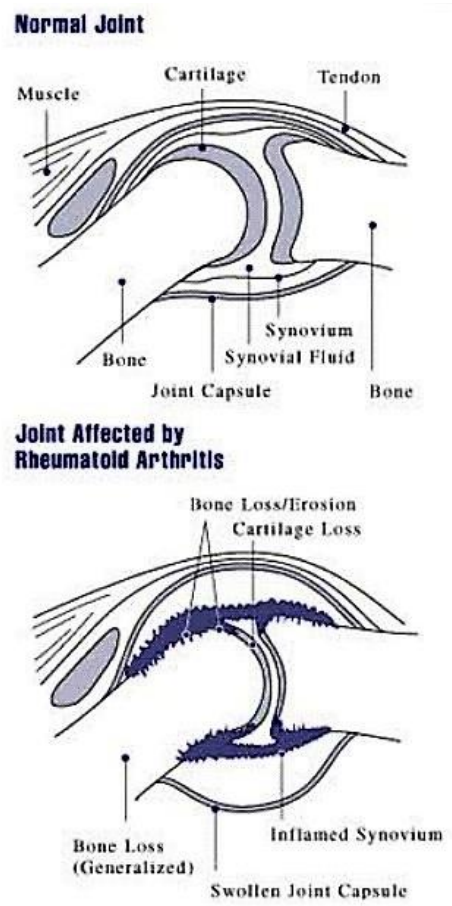


Figure 3: The pathophysiology of Rheumatoid Arthritis

Treatment:

Pharmacological treatment of rheumatoid arthritis can be divided into

- Disease modifying anti-rheumatic drugs.
- Anti-inflammatory agents and analgesics.
- $DMARD_S$ have been found to produce durable remissions and delay or halt disease progression. In particular they prevent bone and joint damage from occurring secondary to the uncontrolled inflammation.

Disease modifying anti-rheumatic drugs (DMARDS):

DMARDS can be further subdivided into Xenobiotic agents and biological agents. Xenobiotic agents are those DMARDS that do not occur naturally in the body, as opposed to biological.[22]

Xenobiotics include:

Azathioprine, Cyclosporine, D-penicillamine, gold salts, Leflunomide, Minocycline, Hydroxychloroquine, Methotrexate, and Sulfsalazine.

Biological agents:

Tumor necrosis factor (tnf α) blockers - Etanercept (Enbrel), Infliximab (Remicade),

Interleukin-1 blockers - Anakinra

Anti-B cell (CD20) antibody - Rituximab

Anti-inflammatory agents and analgesics:

The treatment of arthritic conditions relies on medicines tht fight joint swelling, stiffness and pain. Circadian rhythm affects the arthritic medication. NSAIDS reduce the swelling, stiffness and pain of arthritis. Taking the medicines at the wrong time of day compromises their effectiveness and increases the risk of side effects such as indigestion, stomach ulcers, headache, anxiety and dizziness. Chronotherapy provides ways of increasing the effectiveness and safety of arthritic medications.

Anti-inflammatory agents include,

A. Glucocorticoids:

Non steroidal anti-inflammatory drugs also act as analgesics.

B. Non steroidal anti-inflammatory drugs:

NSAIDs are drugs with analgesic, antipyretic and anti-inflammatory effects that reduce pain, fever and inflammation. The term "non steroidal" is used to distinguish these drugs from steroids, which (among a broad range of other effects) have a similar eiconsid depressing, anti-inflammatory action.[23]

Mechanism of action:

Most NSAIDs act as non selective inhibitors of the enzyme cyclooxygenase, inhibiting both the cyclooxygenase-1 (COX-1) and cyclooxygenase-2 (COX-2) isoenzymes.

Cyclooxygenase catalyzes the formation of prostaglandins and thromboxane from arachidonic acid (Derived from the celluar phospholipid bilayer by phospholipase A2).

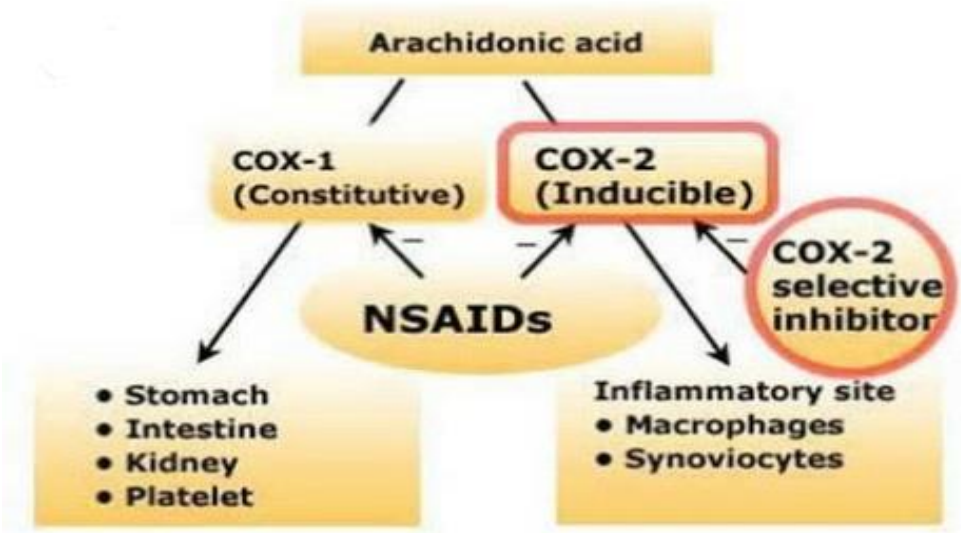


Figure 4: Mechanism of action of NSAIDs

Classification of NSAIDS:

A. Chemical classification:

Table 1: The structural Classification of NSAIDS

S.No.	Chemical Class	Examples
1.	Salicylates	Aspirin
2.	Quinolines	Cinchophen
3.	Pyrazoles	Phenyl butazone
4.	Indolines	Indomethacin, Eltenac, Tepoxalin
5.	Propionic acid	Ibuprofen, ketoprofen
6.	Anthranilic acids	Flunixin, Meclofenamic acid, Tolfenamic acid
7.	Oxicams	Piroxicam, Tenoxicam, Meloxicam
8.	Sulphonamide Derivatives	Nimesulide
9.	Coxibs	Celecoxib, Rofecoxib,Valdecoxib, Parecoxib
10.	Aryl propionic acid	Naproxen

B. Classification based on COX selectivity:

1. Non COX selective NSAIDS:

   Aspirin, Indomethacin, Diclofenac

2. Preferential COX-2 inhibitors:

   Nimesulide, Meloxicam, Nabumetone, Ibuprofen

3. Highly selective COX-2 inhibitors:

   1st generation : Celecoxib, Rofecoxib

   2nd generation : Valdecoxib, Parecoxib, Etoricoxib.[23]

Need for developing the Ibuprofen as Sustained release tablet:

Several reasons are there for attractiveness of sustained release drug delivery system, it provides increased bioavailability, reduction in the frequency of administration, reduces the fluctuation of plasma concentration and side effects and possibly improves the specific distribution of the drug. From this the sustained release formulation of Ibuprofen by solid dispersion technique, promising way to improve the patient compliance by reducing dosing interval and minimizing adverse effect.

AIM AND OBJECTIVE

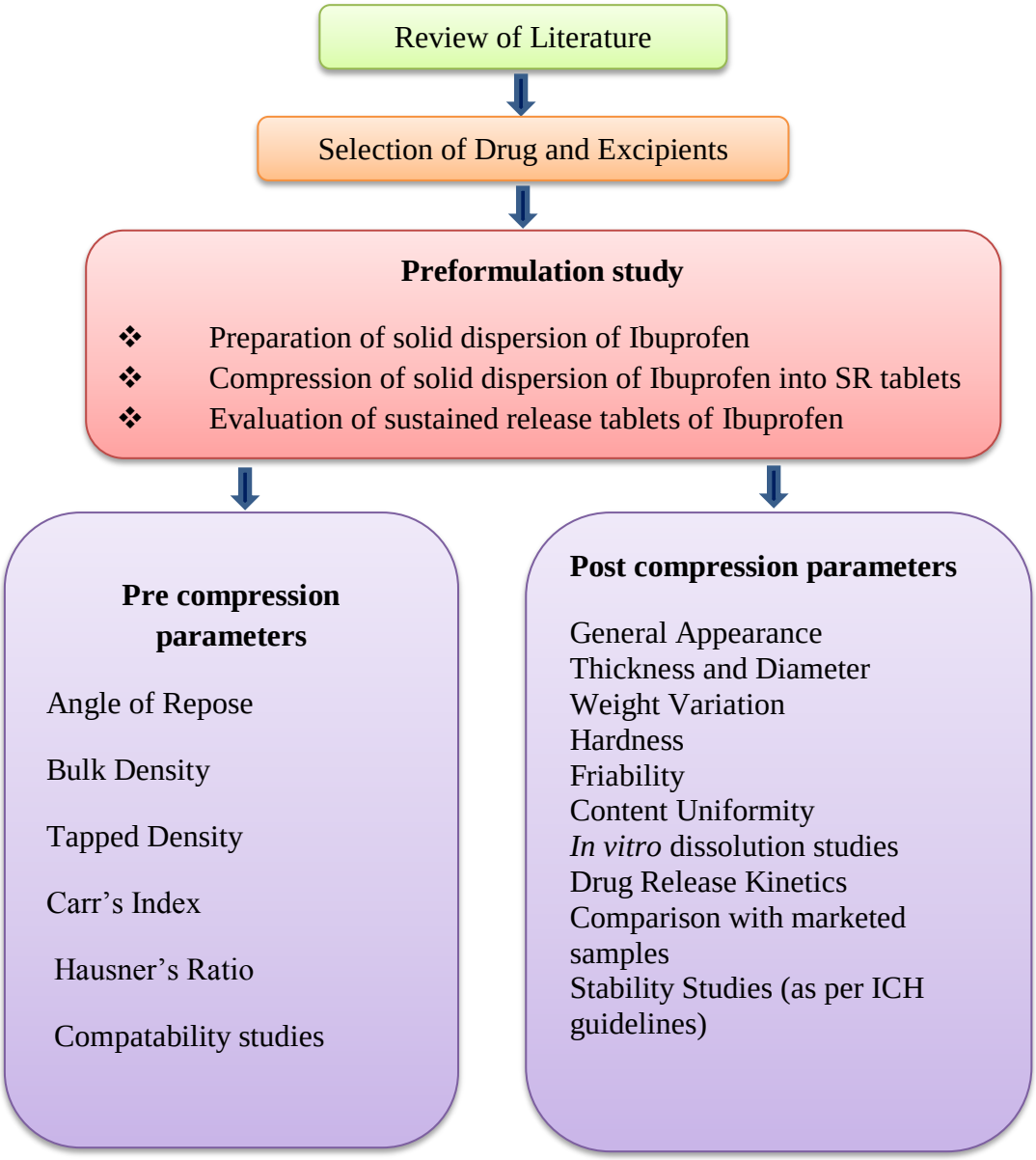
AIM:

The aim of the present study is to formulate and evaluate the sustained release tablets of Ibuprofen by solid dispersion technique.

OBJECTIVE:

- To prepare the solid dispersion of Ibuprofen.
- Drug excipients interaction by FTIR studies.
- Formulation of sustained release tablets of Ibuprofen solid dispersion with concentration of rate controlling polymers like HPMCK4MCR, HPMCK100MCR.
- The formulated tablets are evaluated for weight variation, hardness, friability, drug content, *in vitro* dissolution study, study of release kinetics.
- To perform stability studies as per ICH guidelines.

PLAN OF WORK


Review of Literature
Selection of Drug and Excipients
Preformulation study
❖ Preparation of solid dispersion of Ibuprofen
❖ Compression of solid dispersion of Ibuprofen into SR tablets
❖ Evaluation of sustained release tablets of Ibuprofen
Pre compression parameters
Angle of Repose
Bulk Density
Tapped Density
Carr's Index
Hausner's Ratio
Compatability studies
Post compression parameters
General Appearance
Thickness and Diameter
Weight Variation
Hardness
Friability
Content Uniformity
In vitro dissolution studies
Drug Release Kinetics
Comparison with marketed samples
Stability Studies (as per ICH guidelines)

LITERATURE REVIEW

Kimia Fazaeli Kahkeshan *et.al.,* studied solid dispersion technique: methods and polymers to increase the solubility of poorly soluble drugs. Solid dispersions in water-soluble carriers have engrossed considerable interest as a means of improving the dissolution rate and bioavailability of hydrophobic drugs. Although solid dispersions have tremendous potential for improving drug solubility and only a few marketed products using this approach. A solid dispersion generally composed of two components the drug and the polymer matrix. Numerous methods are existing to prepare the solid dispersions such as melting method, spray drying method, co-grinding method, lyophilisation technique, hot melt extrusion, melt agglomeration, super critical fluid technology etc. A variety of hydrophilic carriers have been investigated for enhancement of dissolution characteristics and bioavailability of poorly aqueous soluble drugs.[18]

Meka Anand Kumar *et.al.,* developed and evaluation of the solid dispersion formulated ibuprofen tablets using cyclodextrins as a carrier. In the present investigation, an attempt was made to increase the therapeutic effectiveness of ibuprofen, by increasing the solubility, via solid dispersion using beta cyclodextrin (β-CD) and 2- hydroxyl propyl beta cyclodextrins (2-HPβ-CD) as carrier. Eight solid dispersion formulations of ibuprofen were prepared by using different drug: polymer ratios viz. 1:0.5, 1:1, 1:2, and 1:3 for (2-HPβ-CD) and β cyclodextrin by co-evaporation method and optimized solid dispersions were evaluated for drug content, In-vitro release studies, FTIR, differential scanning calorimeter (DSC). No interaction between ingredients was confirmed by FTIR, DSC. The formulation with better drug release was selected and compressed into tablet with weight equivalent to ibuprofen of 400mg.the compressed tablet were evaluated for its hardness, disintegration, weight variation, friability and drug content, compared with marketed tablets and finally loaded for stability at 40ºC/75%RH and the results found to satisfactory.[29]

Gul Majid Khan *et.al.,* prepared and evaluation of solid dispersions of ibuprofen using glucosamine HCL as a carrier. Ibuprofen is sparingly water-soluble drug and has low bioavailability, so to enhance its solubility and improve bioavailability solid dispersions with different drug to carrier ratios (1:1, 1:2, and 1:3) were prepared, as solid dispersion is the most effective method for enhancing the solubility and improving the bioavailability of poorly sparingly water-soluble drug. In this study glucosamine HCL was used as a potential hydrophilic carrier to improve the solubility, dissolution rate and bioavailability of poorly water-soluble drug, Ibuprofen from physical mixtures and solid dispersions. Solid dispersions with different drug to carrier ratios were prepared, using solvent evaporation method. Physical mixtures of ibuprofen and Glucosamine HCL were also prepared for comparison.[30]

Rupali S.Joshi *et.al.,* developed and validation of UV spectrophotometric method's for simultaneous estimation of Ibuprofen. The concentration range between 5-30µg/ml and absorbance maximums at 222.4nm respectively. Methods are validated according to ICH guidelines and can be adopted for the routine analysis of ibuprofen in pure and tablet dosage form.[31]

Hapse S.A *et al.,* studied simple, sensitive and specific spectrophotometric method were developed and validated for quantification of ibuprofen by difference spectroscopy. Ibuprofen exhibits a substantial difference in absorbance in the two solvents that is in 0.1 N HCL and 0.1 N NaoH at 222nm. Beer's law was obeyed in the concentration range of 5 to 40 µg/ml for ibuprofen. Results of tablet analysis showed standard deviation in the range of 0.3694 to 1.851 for ibuprofen which indicate repeatability of the method. The results indicated excellent recoveries ranging from 101.13 to 101.23% for ibuprofen with a mean of 101 %. Recoveries obtained do not differ significantly from 100% showed that there was no interference from the common excipients used in the tablet formulation indicating accuracy and reliability of the method.[32]

Yousry M. Issa *et al.,* studied simple, rapid and accurate new method is described for the simultaneous determination of ibuprofen and paracetamol in two components mixture and cetofen tablets. The method depends on the derivatives of the ratio spectra DD by measurement of the amplitude of DD at 225.6 nm and the amplitude of DD at 238.9 nm for IB and PA. Calibration graphs are linear in the range 2-32 (LOD 0.53) and2-24 (LOD 0.57) µg/ml IB and PA, respectively. The proposed method is successfully applied for simultaneous determining IB and PA in authentic mixtures and cetofen tablets.[33]

Hugo Almeida *et al.,* Studied prolonged- release solid dispersions of ibuprofen. Ibuprofen (IB) is the one of the most important non-steroidal anti-inflammatory drugs used in the treatment of inflammatory chronic diseases. This drug presents, in pure state, poor physical and mechanical characteristics and their use in solid dosage forms needs the addition of excipients which improve these properties. The selection of the best excipients and the suitable pharmaceutical dosage form to carry ibuprofen are very important for the industrial success of this drug. Solid dispersions of ibuprofen with stearic acid and hydrogenated castor oil showed better flow characteristics than pure ibuprofen and the respective physical mixtures. Gelatin capsules filled with solid dispersions were submitted to dissolution tests in order to study the influence of the prepared systems in the release profiles of ibuprofen. Prolonged-release of ibuprofen was achieved with the solid dispersions prepared with the different types of excipients.[39]

R.Margret chandira *et al.,* formulated and evaluation the oral tablets Ibuprofen. The purpose of the study is to investigate the effect of roller compaction (RC) parameter (auger speed) on the properties of flakes, granules and tablets. This study is carried out in six formulation preparing by changing auger speed(6-7, 10-11, 14-15, 18-19, 23-24, 27-28 rpm) of roller compactor resulting in flakes of different hardness were prepared, and its impact on the flow

properties(bulk density, tapped density) of the granules and finally its effect on the properties of tablet such as hardness, thickness, friability. For this study ibuprofen is the model drug selected and the tablets formed by changing the auger speed is of ibuprofen. In this study the tablet's in vitro drug release were also performed and compare with the marketed ibuprofen tablet.[40]

M.M.Gupta *et al.,* studied enhancement of dissolution rate of ibuprofen by preparing solid dispersion using different methods. Ibuprofen is absorbed rapidly, bound avidly to protein, but it has low aqueous solubility so, it also lowers the dissolution profile of drug ibuprofen was increased by preparing solid dispersion with urea in ratio of (1:1),(1:3) and (1:5) by using melt dispersion method and solvent evaporation method. The rate of dissolution of ibuprofen was increased with the proportion of (1:5) when compared to other formulations.[41]

Abhik kar *et al.,* enhancement of solubility and dissolution of ibuprofen by solid dispersion technique and formulation of sustained release tablets containing the optimised batch of solid dispersion. Solid dispersions of ibuprofen were prepared by using PEG 20000 and poloxamer 407 in different weight ratios by fusion and solvent evaporation method. Drug-carrier physical mixtures were also prepared. Solid dispersions were characterized by saturation solubility, drug content, *in-vitro* dissolution, FTIR and DSC analysis. Sustained release tablets containing the solid dispersion granules the optimized batch were prepared by direct compression method. The prepared formulations were evaluated for hardness, thickness, weight variation, friability, *in-vitro* dissolution studies and release kinetic modelling.[47]

Madhuri Newa *et al.,* were prepared and evaluation of fast dissolving Ibuprofen Polyethylene Glycol 6000 solid dispersions. To improve its oral absorption, rapidly dissolving ibuprofen solid dispersions were prepared in a relatively easy, simple, quick, inexpensive, and reproducible manner, characterized by scanning electron microscopy(SEM), differential scanning

calorimetry(DSC), and Fourier transform infrared spectroscopy(FTIR). They were evaluated for solubility, in vitro drug release, and oral bioavailability of ibuprofen in rats. Quicker release of ibuprofen from SD_S in rat intestine resulted in a significant increase in AUC and C_{max}, and a significant decrease in T_{max} over pure ibuprofen. Preparation of fast- dissolving ibuprofen SD_S by low temperature melting method using PEG 6000 as a meltable1 hydrophilic polymer could be a promising approach to improve solubility, dissolution, and absorption rate of ibuprofen.[48]

Sundar *et al.*, designed and evaluation of sustained release tablets containing Solid dispersion of Ziprasidone hydrochloride. Ziprasidone hydrochloride solid dispersions were prepared with PEG 6000 and β-cyclodextrin. The efficient dispersions was further directly compressed to sustained release tablets with matrix polymers like guar gum and HPMC K15 in the ratios of 1:0.5, 1:1, 1:1.5. Pre compression and post compression parameters were carried out along with compatibility studies and *in vitro* drug release studies. The influence of polymers on the release rate and mechanism of drug release for Ziprasidone hydrochloride from matrix tablets were determined. The mechanism of release of drug from the formulations was observed to be diffusion controlled exhibited by higher correlation with Higuchi kinetics. To confirm the exact mechanism of drug release from these tablets, the data were fitted to Korsemeyer-peppas equation. Slope values >0.5 suggested that the release of Ziprasidone hydrochloride from the sustained release solid dispersion tablets revealing the fickian drug transport mechanism.[49]

Suja C Jayan *et al.,* formulated and evaluation of ibuprofen tablets using Gum of Anacardium Occidentale as binding agent. Anacardiumgum derived from the edible seeds of Anacardiumoccidantale(family Anacardiaceae) was evaluated for its binding properties at a concentration of 5% w/w and 10%w/w in ibuprofen

tablets with official starch as a control. The hardness, disintegration time and dissolution rate increased with increase in concentration of Anacaediumgum. Tablets containing 10%w/w of Anacardiumgum had a binding capacity approximately twice that of starch with a dissolution rate of 58.5% after 30 min.[50]

Sachin K Gawai *et al.,* studied *In vivo-In vitro* evaluation of solid dispersion containing Ibuprofen. Solid dispersion technique can be used to enhance the solubility, dissolution rate and absorption of several insoluble drugs. The different solid dispersion methods were studied using PEG 6000 as carrier. Tests of physical evaluation, drug content, loss drying and *in vitro* dissolution were carried out. *In-vivo* anti- inflammatory activity of 1:2 ratio formulation of fusion method shows highest dissolution and absorption rate than marketed preparation. The present study concluded with the importance of solid dispersion technique and their methods in enhancing the solubility of poorly water soluble drug.[51]

M.Sunitha Reddy *et al.,* formulated and evaluation of ibuprofen sustained release matrix tablets using Manlikara Zapota Gum as a release retarding polymer. Properties of plant gum obtained from sapota fruit were studied. Physicochemical characterization of the gum was done by carrying out solubility test, loss in drying, total ash, pH determination, swelling characteristics and micromeritic properties. *In-vitro* drug release studies were carried out in pH buffer-7.2 for 12 hours. Effect of gum in different concentrations on release kinetics evaluated. The total ash and acid insoluble value of Manlikara Zapota gum was found to be 2.28 and 1.0 % w/w respectively. The swelling index is high in distilled water followed by phosphate buffer. Due to the short half-life (2-4hrs), an ibuprofen sustained release tablets were prepared by wet granulation method using Manlikara Zapota gum as a retarding polymer. The dissolution studies were performed using U.S.P apparatus type-2 using pH 7.2 phosphate buffers as dissolution medium. These

studies showed that formulation consisting of polymer was found to sustain the release of ibuprofen over a period of 12hrs. Manlikara Zapota gum as binder was of good mechanical strength and acceptable friability values. This implies that the gum can be used for intestinal drug delivery. Formulation was subjected to different kinetic models including zero order, first order, higuchi model, and korsemeyer peppa's model and the formulation was found to follow first order kinetic model. The final optimized formulation was subjected to accelerated stability for 3 months according to I.C.H guidelines.[52]

Mohammed Omar *et al.,* formulated and in vitro evaluation of immediate release tablets of fenofibrate solid dispersions by different techniques. Fenofibrate BCS class II Anti hyperlipidaemia drug belongs to fibrate class was formulated as solid dispersions by using various hydrophilic carriers to enhance the solubility, dissolution rate and oral bioavailability. Solvent evaporation method, Fusion Method, and Melt solvent method are used to prepare solid dispersions of fenofibrate. To develop the solid oral dosage form (Tablets) with fenofibrate solid dispersions. To study the physical parameters of tablets of tablets prepared by direct compression, which includes hardness, friability, weight variation, and disintegration. To estimate the % drug content in the solid dispersions and the fabricated formulations. To evaluate the drug release from the tablets by in-vitro dissolution studies and to compare in vitro dissolution profile of fabricated formulation with marketed formulation.[53]

Bhawandeep Gill *et al.,* studied glimepiride is poorly water soluble drug, so solubility is the main constraint for oral its bioavailability. An attempt has been made to increase the solubility of this model drug by formulating solid dispersion using polaxmer 188 as polymer and then formulating SD_S tablets of the best formulation of SD_S. Tablet formulations were prepared by direct compression technique using superdisintegrant croscarmellose sodium in different

concentrations. SD containing drug is to polymer ratio 1:4 gives best dissolution profile and dissolution efficacy and among tablet formulations, formulations containing 5% croscarmellose sodium gives best disintegration and dissolution profiles compared with other formulations. Results showed that polaxmer is a promising polymer for enhancing the solubility of GMP.[55]

M Gopal Rao *et al.,* prepared and evaluation of Solid dispersions of Naproxen using carriers such as PVP, PEG 4000, PEG 6000, PEG 20000, methylcellulose and β-Cyclodextrin with a view to develop fast release formulations of Naproxen. Solid dispersions of naproxen were prepared by solvent evaporation method and the dispersions were evaluated for drug content uniformity, dissolution rate, moisture absorption, thin layer chromatography, Scanning electron microscopy, and X-ray diffraction analysis. A marketed increase in dissolution rate. All the solid dispersions except naproxen-PVP were found to be non-hygroscopic. Naproxen was found to be in an amorphous form in solid dispersions. Selected dispersions of Naproxen-β-Cyclodextrin and Naproxen-methylcellulose were formulated into capsules with usual additives and evaluated for drug release characteristics.[57]

M. Mohan Varma and P. Sathish Kumar formulated and evaluation of Gliclazide tablets containing PVP-K30 and Hydroxyl-β-cyclodextrin solid dispersion technique. Solid dispersions were prepared using PVP-K30 and Hydroxypropyl-β-cyclodextrin as the hydrophilic carriers. The solid dispersions were characterized by using DSC, XRD and FT-IR. The formulated tablets were evaluated for the quality control parameters and dissolution rates. The optimized formulation showed a 3 fold faster drug release compared to the branded tablet. The XRD studies demonstrated the remarkable reduction in the crystallinity of the drug in the solid dispersion. The faster dissolution rate of the drug from the solid dispersion is attributed to the marked reduction in the crystallinity of the drug. The

DSC and FTIR studies demonstrated the absence of the drug-polymer interaction.[66]

Anusha Pagadala *et al.,* studied formulation and evaluation of solid dispersion of solid dispersion of Glimepiride in to sustained release. Solid dispersions of glimepiride were prepared by using Urea and PEG 6000 as carrier in drug: carrier 1:1, 1:2, 1:3, 1:4 ratios by fusion method. From these all solid dispersions formulation SDUF3 containing Urea shows better dissolution compared to other solid dispersions. This optimized solid dispersion is formulated into sustained release tablets by direct compression method using hydroxyl propyl methyl cellulose and ethyl cellulose polymers.[67]

Syed Shariff Miyan *et al.,* designed and development of fast dissolving tablets of Gliclazide by solid dispersions technique. The solubility of poorly soluble drug was enhanced by preparing solid dispersions of the drug with PEG 6000 in various concentrations. The optimized solid dispersions (Drug: PEG 6000 1:2 ratio) were further kneaded with suitable proportions of superdisintegrants such as; Crosscarmellose, Sodium starch glycolate and Crosspovidone. Fast dissolving tablets of Gliclazide was prepared by direct compression method. The pre-compressive parameters for the blends and post –compressive parameters for the prepared tablets were evaluated. Short term accelerated stability study was performed for optimized formulation and found no evidence of physical and chemical changes. FTIR study showed no evidence of drug-excipient interaction. The optimized formulation was found to be FDTG. It was concluded that fast dissolving tablets of Gliclazide can be prepared by solid dispersions of drug with PEG-6000 and combination of two superdisintegrants provide complete and better dissolution within in shorter period of time.[68]

S.L.Neha *et al.,* formulated and sustained release solid dispersion of Metoclopramide HCL by solvent evaporation method. Several polymers like

combination of Eudragit RSPO, Eudragit RLPO and Guargum. Egg albumin as synthetic and natural polymers respectively were used. The *In vivo* studies were performed on Albino Wistar rats and various pharmacokinetic parameters were determined. The whole study was showed that the solid dispersion of Metoclopramide HCL sustained the release rate of drug for a prolong period of time at least 12hrs and shows to increase the bioavailability and simultaneously decrease the dosing interval as well as dosing amount. The formulation minimizes the blood level oscillations, dose related adverse effects and cost of ultimately improve the patient compliance and drug efficiency.[69]

Kenechukwu FC *et al.,* studied characterization and *In vivo* evaluation of Ibuprofen-PEG 8000 solid dispersion were prepared by fusion method using varying combination ratios 1:1,1:2, 1:3, and 1:4. Characterization based on surface morphology, particle size, absolute drug content, FTIR and micromeritic properties were carried out on the SD_S. The *in vivo* release of Ibuprofen from SD_S was performed using rats. The FT-IR results indicate no strong chemical interaction of Ibuprofen and PEG 8000 in the SD_S. Administration of the SD_S to rats resulted in much higher plasma concentration compared to the pure Ibuprofen and physical mixture ($p<0.05$), an indication of enhanced absorption rate of Ibuprofen in the SD_S systems. This study has shown that Ibuprofen-PEG 8000 SD_S could offer a better and more effective approach of increasing the dissolution and absorption rate of the drug.[70]

Jani Rupal *et al.,* prepared and evaluation of solid dispersions of Aceclofenac by solvent evaporation method. Dissolution of Aceclofenac increased with increase in the proportion of carriers (1:1, 1:5, and 1:9). Of both the carriers used, dissolution of the aceclofenac could be improved by solid dispersion and PEG 6000 based solid dispersions were more effective in the enhancing the dissolution.[71]

Fayeza Tahseen A.B.Gangurde, formulated and development *In-vitro* evaluation of sustained release tablets of Carvedilol solid dispersion technique for improving solubility of Carvedilol using Poloxamer 407 and PVP K30. The Carvedilol tablets were prepared by direct compression method using HPMC K15 as sustained release polymer in different concentrations. The prepared tablets were evaluated for various physiochemical parameters, *n-vitro drug* release study was carried out in simulated gastric fluid (0.1 N HCL) for the first 2hr and in phosphate buffer (pH 6.8) for the next 12hr following USP Type II paddle apparatus. Increase in HPMC concentrations resulted in a significant decrease in Carvedilol release. For instance, the tablets containing 20mg of HPMC K15 (F1 and F4) shows 97% drug release upto 12hr when compared to 40mg and 60 mg of HPMC K15(F2,F3,F5, and F6) shows 98% drug release upto 14hr. The *in-vitro* data is fitted in to different kinetic models like Zero order, First order, Korsmeyer and Higuchi's plot. The release of Carvediolol from the tablets containing solid dispersions of Poloxamer 407 and PVP K30 were shown early $t_{50\%}$ 6.4hrs(F1 and F4) than it's plane drug tablet formulation 9.5hrs (F7). From this study, it was clarified that solid dispersion technique was one of the promising sustained release system applying for poorly water soluble drugs.[72]

S Kumar and Satish Kumar Gupta, prepared and evaluation of solid disersions of Aceclofenac for the improvement of dissolution rate. The present work aims to prepare the solid dispersions of Aceclofenac by solvent wetting method by using potato starch as carrier in the ratios of 1:1 and 1:2 formulated solid dispersions were characterized for 1% practical yield, carr's index, angle of repose, Hausner's ratio, drug content and *in vitro* drug dissolution. *In vitro* release study has shown that there is an enhancement in the release rate of aceclofenac from all prepared batches in comparison to pure aceclofenac. Experimental results showed that formulation F2(1:2 ratio of drug: potato starch, prepared by solvent wetting method) showed more release in comparison to other batches.[73]

Ganesh Chaulang *et al.,* prepared and characterization of solid dispersion tablet of Furosemide with Crospovidone by using Kneading technique. 1:1(w/w) and 1:2 (w/w) solid dispersions were prepared by kneading method using solvent water and ethanol in 1:1 ratio. Dissolution studies, FTIR, DSC, and X-ray diffractometry were performed to identify the physicochemical interaction between drug and carrier, hence its effect on dissolution. Tablets containing solid dispersion exhibited better dissolution profile than commercial tablets. Thus, the solid dispersion technique can be successfully used for improvement of dissolution of Furosemide.[74]

S.K Swain *et al.,* designed and evaluation of sustained release solid dispersion of Verapamil Hydrochloride. The results obtained showed that the rate of dissolution of Verapamil hydrochloride was considerably more sustained when formulated in solid dispersions with HPMC K4M and Eudragit RSPO as compared with pure drug and physical mixtures. FT-IR studies confirmed absence of any possible solid state drug and polymer interactions. In order to establish the mechanism and kinetics of drug release, the experimental data was fitted to different kinetic models like Zero order, First order, Higuchi model, Korsmeyer peppa's model. From the above research it may be concluded that HPMCK4M acts as a better release retardant for the model drug.[75]

Samba Moorthy.U *et al.,* formulated Sustained release of solid dispersions of Verapamil Hydrochloride using Ethyl cellulose and Eudragit-RSPO. In present study the SD's containing EC and Eudragit-RSPO at different drug-polymer ratios of 1:0.5, 1:1, 1:2, 1:3. 1:5,1:7, 1:7:0.75, 1:7:0.5, 1:7:0.75 as F1-VPH:EC, F2-VPH:EC, F3-VPH:EC, F4-VPH:RSPO,F5-VPH:RSPO, F6-VPH:RSPO, F7-VPH:EC:RSPO, F8-VPH:EC:RSPO, F9-VPH:EC:RSPO respectively by solvent evaporation technique. The physical mixtures were prepared by physical mixing technique at the same ratio as solid dispersion. The physical mixtures were prepared by physical mixing technique at the same ratio as

solid dispersion. FTIR spectroscopy suggested that there was no major interaction between drug and polymers. The *in-vitro* release profile indicates that the release of VPH can be effectively controlled from a tablet containing S.D. The release data was analysed as per the peppa's equation model indicating that the non-fickian diffusion was the release mechanism.[76]

Kosika Sandeep formulated and evaluation of sustained release tablets from solid dispersion of Glipizide. The object of present study is to increase the solubility of Glipizide to enhance the bioavailability and to extent the release of drug. Natural polymers are xanthan gum, Guargum were used to sustain the release of the drug. Drug and excipient study show that no interaction between polymers and drugs. The tablets were evaluated for physical characteristics like hardness, weight variation, friability and thickness. It was found that drug release rate decreased with the amount of polymer increased in formulation. Use of xanthan gum as sustained material drug release is influenced. Magnesium sterate, talc were used to increase the flow property of the powder blend. Based on dissolution studies F5 showed sustained release of drug.[77]

Patil SA *et al.,* formulated and evaluation of extended release solid dispersion of Metformin Hydrochloride using methocel K100M as the carrier by solvent evaporation and cogrinding method. The influence of drug polymer ratio on drug release was studied by dissolution tests. Characterization was performed by FTIR, UV, DSC and X-ray powder diffractometry. The optimized formulation was subjected to accelerated stability testing as per ICH guidelines. Release data were examined kinetically. SD with 1:4 and 1:5 ratio of drug to polymer obtained by solvent evaporation and cogrinding were selected as the best candicates suitable for prolonged-release oral dosage form of metformin.[78]

K. Arun Prasad *et al.,* prepared and evaluation of solid dispersion of Terbinafine Hydrochloride by using carriers polyethylene glycol 6000 (by melting method) and polyvinyl K 30(by solvent method) in the drug carrier ratio of 1:1, 1:2 and 1:3. The prepared solid dispersions were characterized for their drug content, thermal studies, infrared spectral studies, differential scanning calorimetric studies, aqueous solubility studies and *in-vitro* release studies. From the results, it was clear that solid dispersion formulation showed improved dissolution rate than pure drug and physical mixture. The solid dispersion showing better release profile was chosen to formulate into a tablet dosage form weight 600mg. The tablets compressed were evaluated for its physical parameters like thickness, hardness, weight variation, friability, drug content and disintegration tests. The dissolution profile of formulated tablet was compared with marketed product and the formulated tablet showed better release profile than the marketed product. [79]

Rajeshree Panigrahi *et al.,* studied Enhancement of solubility of Gliclazide by solid dispersion. The enhancement of oral bioavailability of poorly water-soluble drugs remains one of the most challenging aspects of drug development. Solid dispersions must be developed into convenient dosage forms, such as capsules and tablets, for their clinical use and successful commercialization. The initial solubility of pure drug Gliclazide was found to be 8µg/ml. Solid dispersion of Gliclazide was prepared using Polyethylene glycol 4000, Polyethylene glycol 6000, Mannitol, Low substituted Hydroxy propyl cellulose as carriers by kneading, Solvent evaporation and Solusorb method respectively. Different ratios 1:1, 1:3, 1:9 of drug: carrier is taken. The maximum enhancement of solubility was found in kneading method of ratio 1:1 using drug: low substituted hydroxyl propyl cellulose with 250%.[80]

DRUG PROFILE

IBUPROFEN:

Ibuprofen is a medication in the non-steroidal anti-inflammatory drug (NSAID) class that is used for treating pain, fever, and anti-inflammation. This includes painful menstrual period, migraines, and rheumatoid arthritis. About 60% of people improve with any given NSAID, and it is recommended that if one does not work then another should be tried. It may also be used to close a patent dectus arterious in a premature baby. It can be used by mouth or intravenously. It typically begins working within an hour.

Common side effects include heartburn and a rash. Compared to other NSAID it may have fewer side effects such as gastrointestinal bleeding. It increases the risk of heart failure, kidney failure, and liver failure. At low doses, it does not appear to increase the risk of myocardia infraction; at higher doses it may. Ibuprofen can also result in worsened asthma.it is unclear if it is safe in early pregnancy, it appear to be harmful in later pregnancy and therefore is not recommended. Like other NSAIDSs, it works by inhibiting the production of prostaglandins by decreasing the activity of the enzyme cyclooxygenase. Ibuprofen might be weaker anti-inflammatory than other NSAIDs.[23,25]

PROPRIETARY NAME:

Mortin, Advil, Mortin IB, IBU

SYSTEMIC (IUPAC) NAME:

2-[4-(2-methylpropyl) phenyl] propionic acid

STRUCTURE

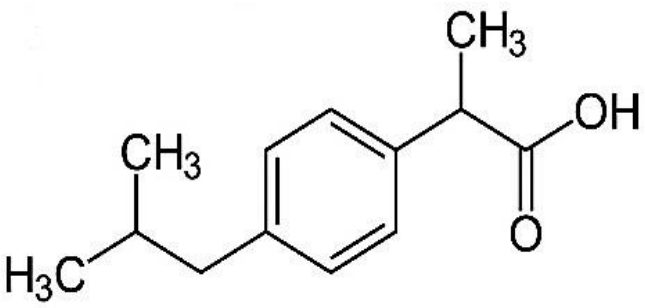


Figure 5: Structure of Ibuprofen

PROPERTIES:

Formula :$C_{13}H_{18}O_2$

Molar mass : 206.29gm/mol

Chirality : Racemic mixture

Density : 1.03g/cm

Melting point : 75 to 78ºC

Boiling point: 157ºC (315ºF)

SOLUBILITY:

Freely soluble in acetone, in chloroform, in ethanol and in ether. Practically insoluble in water. It dissolves in dilute solutions of alkali hydroxides and carbonates.[26]

DECRIPTION:

A white or almost white, crystalline powder or colourless crystals; odour, slight.

INDICATION:

Pain and inflammation in rheumatic disease and other musculoskeletal disorders including juvenile arthritis; mild to moderate pain including dysmenorrheal pain, headache, pain in children, acute migraine attack.

MECHANISM OF ACTION:

Nonsteroidal anti-inflammatory drugs such as ibuprofen work by inhibiting the cyclooxygenase (COX) enzymes, which convert arachidonic acid to prostaglandin H2(PGH2).PGH2 in return, is converted by other enzymes to several other prostaglandins (which are mediators of pain, inflammation and fever) and to thromboxane A2 (which stimulates platelets aggregation, leading to the formation of blood clots).

Like aspirin and indomethacin, Ibuprofen is a non -selective COX inhibitor, in that inhibits two isoforms of cyclooxygenase, COX-1 and COX-2.The analgesic, antipyretic, and anti-inflammatory activity of NSAIDs appear to operate mainly through inhibition of COX-2,which decreases the synthesis of prostaglandins involved in mediating inflammation ,pain, fever and swelling. The antipyretic effects may arise as a result of action on the hypothalamus leading to vasodilation, an increased peripheral blood flow and subsequent heat dissipation. Inhibition of COX-1 instead would be responsible for unwanted effects on the gastro intestinal tract. However the role of the individual COX isoforms in the analgesics, anti-inflammatory and gastric damage effects of NSAIDs is uncertain and different compounds cause different degree of analgesia and gastric damage.

Ibuprofen is administered as a racemic mixture. The R-enantiomer undergoes extensive interconversion to the S- enantiomer in-vivo. The S enantiomer is believed to be the more pharmacologically active enantiomer. The R enantiomer is converted through a serious of 3 main enzymes. These enzyme includes acyl-CoA-synthetase, which converts the R enantiomer to (-)-R-Ibuprofen 1-CoA;2-arylpropinyl-CoA epinerase, which coverts (-)-R-Ibuprofen 1-CoA TO (+)-S-Ibuprofen 1-CoA; and hydrolyse, which converts (+)-S-Ibuprofen1-CoA to the S- enantiomer. In addition to the conversion of ibuprofen to the S enantiomer, the body can metabolize Ibuprofen to several other compounds, including numerous hydroxyl, carboxyl, and glucuronyl metabolites. Virtually all of these have no pharmacological effects.[22, 24]

CATEGORY:

Anti-inflammatory, Analgesic, and Antipyretic

PHARMACOKINETIC DATA:

Bioavailability : 80-100% [by mouth], 87% [rectal]

Protein binding : 98%

Metabolism : Hepatic [CYP2C9]

Half-life : 1.8-2hrs

Excretion : Renal [95%]

CONTRA INDICATIONS:

Hypersensitivity (including asthma; angioedema; urticarial or rhinitis) to acetylsalicylic acid or any other NSAID; active peptic ulceration; for treatment of pre-operative pain in the setting of coronary artery bypass graft surgery; neonates with congenital heart disease.

INTERACTION:

Drinking alcohol when taking Ibuprofen may increase the risk of stomach bleeding. According to the US Food and drug administration (FDA), "Ibuprofen can interfere with the antiplatelet effect of low-dose aspirin less effective when used for cardio protection and stroke prevention." Allowing sufficient time between doses of ibuprofen and immediate-release (IR) aspirin can avoid this problem. The recommended elapsed time between a dose of ibuprofen and a dose of aspirin depends on which is taken first, It would be 30 minutes or more for ibuprofen taken before IR aspirin. However this timing cannot be recommended for enteric coated aspirin. But, if ibuprofen is taken only occasionally without the recommended timing, the reduction of the cardio protection and stroke prevention of a daily aspirin regimen is minimal.

ADVERSE EFFECT

Gastrointestinal disturbances including nausea, diarrhoea, dyspepsia, gastrointestinal haemorrhage; hypersensitivity reaction including rash angioedema; bronchospasm; headache; dizziness; nervousness; depression; drowsiness; insomnia; vertigo; tinnitus; photosensitivity; haematuria; renal failure; fluid retention(rarely, precipitating congestive failure in elderly), raised blood pressure; rarely, hepatic damage; alveolitis, pulmonary eosinophilia; pancreatitis; visual disturbance, skin reaction like dermatitis.

OVER DOSE:

Ibuprofen overdose has become common since it was licensed for OTC use. Many overdose experiences are reported in the medical literature, although the frequency of life threatening complications from ibuprofen overdose is low. Human response in cases of overdose ranges from absence of symptoms to fatal

outcome despite intensive-care treatment. Most symptoms are an excess of the pharmacological action of the ibuprofen, and include abdominal pain, nausea, vomiting, drowsiness, dizziness, headache, tinnitus, and nystagmus. Rarely, more severe symptoms such as gastrointestinal bleeding, seizures, metabolic acidosis, hyperkalaemia, hypotension, bradykardia, tachycardia, atrial fibrillation, coma, hepatic dysfunction, acute renal failure, cyanosis, respiratory depression and cardiac arrest have been reported. The severity of symptoms varies with the ingested dose and the time elapsed; however, individual sensitivity also plays an important role. Generally the symptoms observed with an overdose of ibuprofen are similar to the symptoms caused by overdoses of other NSAIDs.

EXCIPIENTS PROFILE

LACTOSE MONOHYDRATE

Nonproprietary Names

BP : Lactose

JP : Lactose Hydrate

PhEur : Lactose monohydrate

USPNF: Lactose monohydrate

Synonyms

Lactochem, Pharmatose, HMS, NF Lactose, capsuLac, PrismaLac, SacheLac, Sorbolac, SpheroLac, Tablettose, Inhalac.[27]

Chemical Name:

O-β-D-Galactopyranosyl-(1-4)-α-D-glucopyranose monohydrate

Structural Formula:

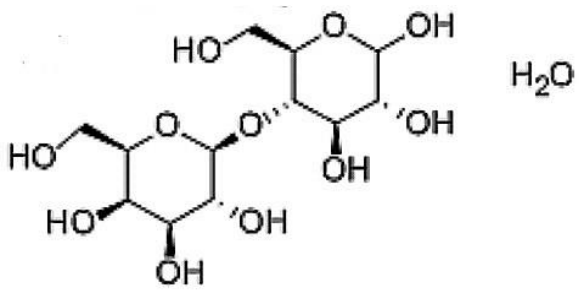


Figure 6: Structure of Lactose monohydrate

Empirical Formula and Molecular Weight:

$C_{12}H_{22}O_{11}H_2O$ 360.31

Description:

White crystalline particles or powder. Lactose is odourless and slightly sweet-tasting.

Functional category

Binding agent; diluent for dry-powder inhalers; tablet binder; tablet and capsule diluent.

Pharmaceutical Application:

[27] Lactose is widely used as filler or diluents in tablets and capsules, and to a more limited extent in lyophilized products and infant formulas. Lactose is also used as a diluents in dry –powders inhalation. various lactose are commercially available that have different physical properties such as particle size distribution and flow characteristics .This permits the selection of the most suitable material for a particular application; for example, the particle size range selected for capsules is often dependent on the type of encapsulating machine used. Usually, fine grades of lactose are used in the preparation of tablets by the wet-granulation method or when milling during processing is carried out, since the fine size permits better mixing with other formulation ingredients and utilize the binder more efficiently.

Other application of lactose includes use in lyophilized products, where Lactose is added to freeze-dried solutions to increase plug size and aid cohesion. Lactose is also used in combination with sucrose to prepare sugar-coating solutions.

Direct-compression grades of lactose monohydrate are available as granulated/ agglomerated α-lactose monohydrate, containing small amounts of anhydrous lactose.

Direct – compression grades are often used to carry lower quantities of drug and this permits tablets to be made without granulation.

Other directly compressible lactose is spray-dried lactose and anhydrous lactose.

Incompatibilities:

A Mail lard-type condensation reaction is likely to occur between lactose and compounds with a primary amine group to form brown, or yellowish-brown-colored products.

Lactose is also incompatible with amino acids, aminophylline, amphetamines, and lisinopril.

Storage:

Lactose should be stored in a well-closed container in a cool, dry place.

POVIDONE

Nonproprietary Names:

BP : Povidone

JP : Povidone

PhEur :Povidone

USP : Povidone

Synonyms:

Kollidon, Plasdone, Polyvinyl Pyrrolidone, Povidonum,povipharm

Empirical Formula and Molecular Weight

$[C_6H_9NO]_n$ 2500-3000000

Chemical Name:

-Ethenyl-2-Pyrrolidinone homopolymer

Structural Formula:

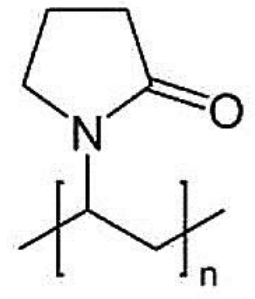


Figure 7: Structure of Povidone

Description:

Povidone occurs as a fine, white to creamy-white colored, odorless or almost odorless, hygroscopic powder.

Functional Category:

Disintegrant, dissolution enhancer, suspending agent, tablet-binder.

Pharmaceutical Application:

Povidone is used in a variety of pharmaceutical formulations; it's primarily used in solid-dosage forms. In tableting, povidone solutions are used as binders in wet-granulation processes.

Povidone is additionally used as a suspending, stabilizing or viscosity-increasing agent in a number of topical and oral suspensions and solutions.

Solubility:

Freely soluble in acids, chloroform, ethanol, ketones, methanol, and water.

Storage:

Povidone stored under ordinary conditions, without undergoing decomposition or degradation. However, since the powder is hygroscopic, it should be stored in an airtight container in a cool, dry place.[27]

Hydroxy Propyl Methyl Cellulose

Nonproprietary Names:

BP : Hypromelleose

JP : Hypromellose

PhEur : Hypromellose

USP : Hypromellose

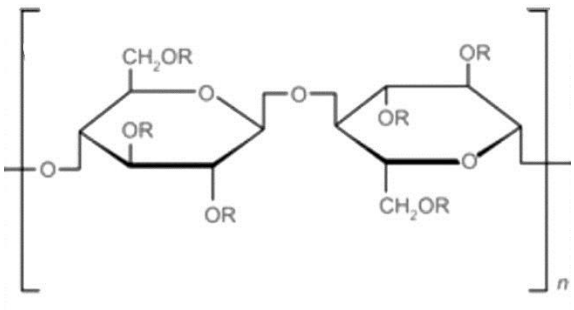
Synonyms:

Benecel MHPC; E464; hydroxyl propyl methylcellulose; HPMC; Methocel; methylcellulose propylene glycol ether ; methyl hydroxy propyl cellulose; Metolose; Tylopur.

Chemical Name:

Cellulose hydroxyl propyl methyl ether

Structural Formula:



Where R is H, CH_3 or $[CH_3CH(OH)CH_2]$

Figure 8: Structure of hydroxyl propyl methyl cellulose

Molecular weight

Molecular weight is approximately 10000-1500000

Description:

Hypromellose is an odorless and tasteless, white or creamy-white fibrous or granular powder.

Functional Category:

Coating agent; film-former; rate-controlling polymer for sustained release; stabilizing agent; suspending agent; tablet binder; viscosity- increasing agent.

Pharmaceutical Application:

Hypromellose is widely used in oral, ophthalmic and topical pharmaceutical formulations. In oral products, hypromellose is primarily used as a tablet binder; in film coating, and as a matrix for use in extended-release tablet formulations. Concentrations between 2% and 5% w/w may be used as a binder in either wet-or dry- granulation processes. High viscosity grades may be used to retard the release of drugs from a matrix at levels of 10-80% w/w in tablets and capsules.

Hypromellose is also used in emulsifier, suspending agent, and stabilizing agent in topical gel and ointments. As a protective colloid, it can prevent droplets and particles from coalescing or agglomerating, thus inhibiting the formation of sediments.

In addition, hypromellose is used in the manufacture of capsules, as an adhesive in plastic bandages, and as a wetting agent for hard contact lenses. It is also widely used in cosmetics and food products.

Viscosity:

Different ranges of viscosity grades are available commercially.

Table 2: Grades of Hypromellose

Methocel product	Nominal viscosity(mPas)
Methocel k100 premium LVEP	100
Methocel k4M premium	400
Methocel k15M premium	15000
Methocel k100M premium	100000

Incompatibilities:

Hypromellose is incompatible with some oxidizing agents. Since it is Non-ionic, hypromellose will not complex with metallic salts or ionic organics to form insoluble precipitates.

Storage:

Hypromellose powder should be stored in a well-closed container, in a cool, dry place.[27]

COLLOIDAL SILICON DIOXIDE

Nonproprietary Name:

BP : Colloidal Anhydrous silica

JP : Light Anhydrous silicic acid

PhEur : Silica colloidal Anhydrous

USP : Colloidal silicon Dioxide

Synonyms:

Aerosil, colloidal silica, fumed silica, fumed silicon Dioxide

Chemical Name:

Silica

Empirical formula and molecular weight:

Sio_2 60.08

Description:

It is a light, bluish-white-colored, odorless, tasteless, amorphous powder.

Functional category:

Adsorbent, anticaking agent, emulsion stabilizer, glidant, suspending agent, tablet disintegrant, thermal stabilizer, viscosity-increasing agent.

Pharmaceutical Application:

Colloidal silicon dioxide is widely used in pharmaceuticals, cosmetics, and food products.[27]

MAGNESIUM STEARATE

Nonproprietary Name:

BP :Magnesium stearate

JP :Magnesium stearate

PhEur :Magnesium Stearate

USP :Magnesium stearate

Synonyms:

Magnesium octadecanoate; octadecanoic acid; magnesium salt; stearic acid.

Chemical Name:

Octadecanoic acids magnesium salt

Empirical Formula and Molecular Weight:

$C_{36}H_{70}MgO_4$ 591.34

Structural formula:

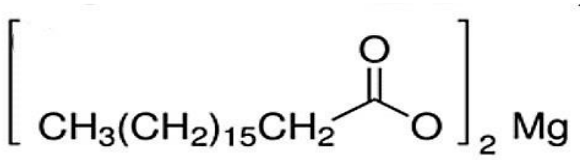


Figure 9: Structure of Magnesium Stearate

Functional Category:

Tablet and capsule lubricant.

Pharmaceutical Application:

Magnesium stearate is widely used in cosmetics, foods, and pharmaceutical formulation. It is primarily used as a lubricant in capsule and tablet manufacture at concentrations between 0.25% and 5.0%W/W. It is also used in barrier creams.

Incompatibilities

Incompatible with strong acids, alkalis, and iron salts. Avoid mixing with strong oxidizing materials. Magnesium stearate cannot be used in products containing aspirin, some vitamins, and most alkaloidal salts.[27]

BETA-CYCLODEXTRIN

Nonproprietary Names:

BP : Alfadex Betadex

PhEur : Alfadex Betadex

USP : Alfadex Betadex

Synonyms:

Beta-cyclodextrin, beta-cycloamylose, beta-dextrin, cyclomaltoheptose, beta dexum.

Chemical Name:

Cyclohepta amylose

Empirical formula and Molecular weight:

$C_{42}H_{70}O_{35}$ 113

Structural Formula:

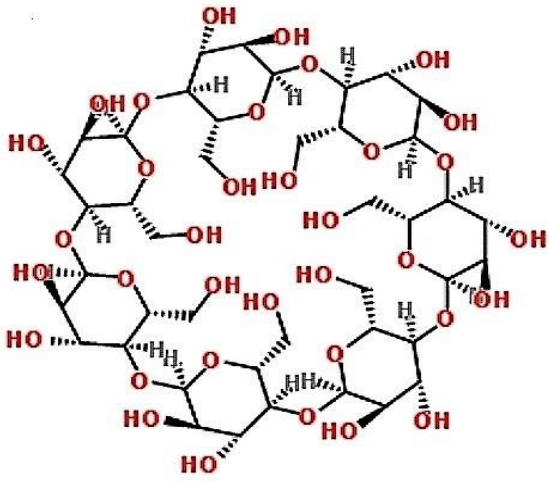


Figure 9: Structure of Beta-Cyclodextrin

Description:

Cyclodextrins occurs as white, practically odorless, fine crystalline powders, having a slightly sweet taste.

Functional category:

Encapsulation agent

Used for increasing the solubility of poorly soluble drugs.

Pharmaceutical Application:

It can be applied widely in the production of medicine, food and cosmetics.

Solubility:

Sparingly soluble in water

Freely soluble in hot water

Slightly soluble in ethanol

Storage:

Stored in a well closed air tight container.[27]

MATERIALS AND INSTRUMENTS

Table 3: MATERIALS

S.No.	Materials	Manufacture
1.	Ibuprofen	Sun Pharmaceuticals
2.	Lactose monohydrate	Hi media Laboratories
3.	Kollidon SR	S.D. Fine Chemicals
4.	HPMCK100MCR	Vijlak Pharma,A.P.
5.	HPMCK4MCR	Vijlak Pharma.A.P.
6.	Aerosil	S.D. Fine Chemicals
7.	Magnesium Stearate	S.D. Fine Chemicals
8.	Beta cyclodextrin	SD Fine chemicals
9	PEG 6000	S.D. Fine Chemicals

Table 4: INSTRUMENTS

S.No.	Instruments	Manufacture
1.	Analytical Balance	Dhona 200D
2.	FTIR Spectrophotometer	Jasco FT-IR 8201 PC
3.	Dissolution Apparatus	Electro lab TDT-08L
4.	Compression Machine	Rimek Mini Press
5.	Differential Scanning Calorimetry	Perkin Elmer, Pyris 6 DSC, Germany
6.	Vernier Caliper	Aerospace 0.2 mm
7.	Hardness Tester	Pfizer Hardness Tester
8.	Friabilator	Roche Friabilator
9.	UV Spectrophotometer	Jasco V530
10.	Disintegration test Apparatus	Electrolab disintegrator
11.	Hot air oven	Thermolab

EXPERIMENTAL SECTION

ANALYTICAL METHOD USED FOR ESTIMATION OF IBUPROFEN BY UV SPECTROPHOTOMETRY

Preparation of Calibration Curve of Ibuprofen in pH 7.2 Phosphate buffer by using the UV method

100mg of ibuprofen was weighed and transfer into a 100ml of volumetric flask and was dissolved in phosphate buffer of pH7.2 and make up to 100ml. This was the standard stock solution containing 1mg/ml of ibuprofen. From this stock solution 10ml was taken and made up to 100ml with phosphate buffer pH 7.2. This was the second standard stock solution (100µg/ml). From this solution dilutions of 10µg/ml, 20µg/ml, 30µg/ml, 40µg/ml, 50µg/ml were made and absorbance was measured at 222nm.

PRE FORMULATION STUDIES

Fourier Transform Infrared (FTIR) studies

The compatibility of drugs and excipients used under experimental condition were studied. The study was performed by taking 2mg sample in 200 mg KBr (Jasco FT-IR8201 PC). The scanning range was 400 to 4000 cm^{-1} and the resolution was $1cm^{-1}$. This spectral analysis was employed to check the compatibility of drugs with the excipients used.

Differential Scanning Calorimetry (DSC)

The differential scanning calorimetry (DSC) of pure drugs, solid dispersion, and the physical mixture of the drug was performed using DSC instrument (Perkin Elmer Pyris 6 DSC, Germany), for the measurement of heat loss or gain resulting from physical or chemical changes within the sample as a function of temperature. About 6-7 mg of the sample was weighed in aluminium DSC pans and hermetically sealed with aluminium lids. An initial ramp was used to jump the temperature to 30ºC and then a constant heating rate of 10ºC/min was used up to 400ºC under nitrogen temperature.

Formulation Development

Preparation Solid dispersion of Ibuprofen

Preparation of solid dispersions of Ibuprofen is to improve the solubility of Ibuprofen and dissolution rate. Solid dispersion of Ibuprofen was prepared by solvent evaporation method. The drug and carrier were mixed in 1:1, 1:2 and 1:3 ratios in ethanol. Solvent was removed by evaporation under reduced pressure. The mass was pulverised and passed through sieve no 60 and stored.

Preparation of physical mixture containing Ibuprofen

The physical mixtures of Ibuprofen-PEG 6000 and Ibuprofen – β -Cyclodextrin in the same weight ratio (1:3) were prepared by thoroughly mixing the appropriate amount of two components for 10 min in a mortar. The mixtures were sieved through a 60 mesh screen and stored in a desiccator for further evaluation. The method of preparation and composition were given Table5.

Table 5: Composition of various batches of Physical mixtures and Ibuprofen Solid Dispersion

Batch Code	Composition	Ratio
$P.M_1$	Ibuprofen: β-Cyclodextrin	1:3
$P.M_2$	Ibuprofen: PEG 6000	1:3
S.D β_1	Ibuprofen: β-Cyclodextrin	1:1
S.D β_2	Ibuprofen: β-Cyclodextrin	1:2
S.D β_3	Ibuprofen: β-Cyclodextrin	1:3
S.D P_1	Ibuprofen: PEG 6000	1:1
S.D P_2	Ibuprofen: PEG 6000	1:2
S.D P_3	Ibuprofen: PEG 6000	1:3

Evaluation of Ibuprofen solid dispersions and physical mixtures

Evaluation studies were carried out by estimating drug content and *in vitro* dissolution studies.

Drug content

The drug content of each solid dispersion batch and physical mixture were determined by UV-spectrophotometry. Accurately weighed quantity of samples from all batches equivalent to 100 mg of Ibuprofen was transferred to a 100ml volumetric flask containing 100ml of phosphate buffer pH 7.2 and the absorbance was measured at 222nm.

***In vitro* dissolution studies**

The prepared solid dispersions were accurately weight equivalent to 100mg of the drug. These solid dispersions are filled in empty capsules and

analysed for drug release in 900ml of phosphate buffer pH (7.2) as dissolution medium at 37± 0.5ºC and 50rpm. 5ml of the sample solution was taken from the dissolution apparatus and the same volume replaced with fresh dissolution medium at predetermined time intervals for 5min. The absorbance of these solutions was measured at 222nm using UV-Visible spectrophotometer.

Preparation of sustained release tablet by using Ibuprofen solid dispersion

Ibuprofen sustained release tablets were prepared by the wet granulation method. Weigh equivalent mg of solid dispersion of Ibuprofen, with other tableting excipients. The blend was mixed with various concentration of rate controlling polymer like HPMC K4MCR, HPMCK100MCR with binder solution. Then the prepared wet mass was passed through Sieve No:60 and dried. The dried granules were mixed with lubricant and compressed into sustained release tablets each weighing about 600mg, by using 12mm punch.

Table 6: Composition of Ibuprofen Sustained release trial tablets

Composition	F1IB (mg)	F2IB (mg)	F3IB (mg)	F4IB (mg)	F5IB (mg)	F6IB (mg)	F7IB (mg)	F8IB (mg)	F9IB (mg)	F10IB (mg)
SD[400mg of Ibuprofen]	480	480	480	480	480	480	480	480	480	480
Lactose monohydrate	30	40	30	20	40	40	30	20	40	30
Kollidon SR	20	20	30	10	30	20	10	20	30	40
HPMC K_4MCR	60	-	50	50	40	-	40	50	-	40
HPMC K_{100}MCR	-	50	-	30	-	50	30	20	40	-
Magnesium stearate	2	2	2	2	2	2	2	2	2	2
Aerosil	8	8	8	8	8	8	8	8	8	8
Total	600	600	600	600	600	600	600	600	600	600

*All the ingredients in mg

Figure 11: Composition of Ibuprofen Sustained release trial tablets

Evaluation of Pre Compression Parameters

The flow properties of the granules were evaluated by determining angle of repose, Bulk density, Tapped density, Compressibility index and Hauser's ratio as mentioned below.[34, 35]

Angle of repose(Ɵ)

Angle of repose is the tan inverse of angle between height (h) of pile of powder and the radius (r) of the base of conical pile. It can be obtained between the freestanding surface of the powder heap and the horizontal plane. The fixed funnel that is secured with its tip at a given height h, above graph paper, placed on the flat horizontal surface. Powder is carefully poured through funnel until the apex of conical pile just touches the tip of funnel.

$$\Theta = \tan^{-1}(h/r)$$

Where,

Ɵ= the angle of repose

h = height of pile

r = radius of base of the pile

Table 7: Relationship between Angle of repose(Ɵ) and Flow properties

Angle of repose(Ɵ)	Flow
25-30	Excellent
30-45	Good
35-40	Fair
40-45	Poor
45-50	Very poor

Bulk density and Tapped density

Both loose bulk density and tapped bulk density were determined. A quantity of 2gm of granules from each formula previously light shaken for the break of any agglomerates formed was introduced into the 10ml of measuring cylinder. After the initial volume was observed, the cylinder was allowed to fall down its own weight from the hard surface from a height of 2-5cm at 2sec intervals. The tapping was continued until no further change in the volume was noted.

LBD and TBD were calculated using the following formula:

LBD: weight of the powder/volume of the packing

TBD: weight of the powder/Tapped volume of the packing

Compressibility index

The compressibility index of the granules was determined by Carr's compressibility index. (%) carr's index can be calculated by using the following formula

Carr's index (%) = [(TBD-LBD) X100]/TBD

Where,

LBD: weight of the powder/volume of the packing

TBD: weight of the powder/Tapped volume of the packing

Table 8: Grading of the powders for their flow properties according to Carr's index

Carr's Index(%)	Flow
5-15	Excellent
12-16	Good
18-21	Fair
23-25	Poor
35-38	Very poor
More than 40	Extremely poor

Hausner's Ratio:

Hausner's Ratio is used to express the compressibility of the powder. It was calculated using the formula

Hausner's Ratio= Tapped Density/Bulk Density

Table 9: Grading of the powders for their flow properties according to Hausner's Ratio

Hausner's Ratio	Flow
1.00-1.11	Excellent
1.12-1.18	Good
1.19-1.25	Fair
1.26-1.34	Passable
1.35-1.45	Poor
1.46-1.59	Very poor
>1.60	Very, very poor

Evaluation of Post Compression Parameters

The formulated tablets tablets were evaluated for the following parameters.[37]

1. General appearance

The general appearance of tablets, its visual identify and overall 'elegance' is essential for consumer acceptance for monitoring the production process.

Size and Shape:

The shape and dimensions of compressed tablets are determined by the type of tooling during the compression process.

2. Uniformity of Thickness

The crown thickness of individual tablet may be measured with a vernier caliper, which permits accurate measurements and provides information on the

variation between tablets. Other technique employed in production control involves placing 5or 10 tablets in a holding tray, where their total crown thickness may be measured with a sliding caliper scale. The tablet thickness was measured using screw gauge.

3. Hardness test

The hardness of the tablets was determined using Pfizer Hardness tester. It is expressed in kg/cm^3 six tablets were randomly picked from each formulation and the mean and standard deviation values were calculated.

4. Friability

The friability of tablets was determined using Roche Friabilator. It is express in percentage (%). Ten tablets were initially weighed and revolved at 25rpm for 4min. the tablets were then reweighed after removal of fines and the percentage of weight loss was calculated by,

$$\%\text{Friability} = \frac{\text{Initial weight-Final weight}}{\text{Initial weight}} \times 100$$

5. Weight Variation

Twenty tablets were selected randomly from each batch and weighed individually on electronic balance. The individual weighed is then compared with average weight for the weight variations. The following percentage deviation in weight variation is allowed. The results are shown in Table10.

% Deviation= Average weight- Individual weight/Average weight×100

Table 10: Percentage weight deviations

Average weight	% difference
130mg or less	10
130-324mg	7.5
324mg and greater	5

6. Drug content Uniformity

Twenty tablets were weighed and its average weight was taken, the powder equivalent to single tablet was dissolved in pH 7.2 phosphate buffer and was transferred to a100ml volumetric flask. After adequate dilutions the absorbance was measured at 222nm.Samples were analyzed by using UV-Spectrophotometer.

7. *In-vitro* dissolution rate studies

The dissolution studies of the Ibuprofen SR tablets were performed using USP dissolution testing apparatus II (paddle type). Using 900ml of phosphate buffer pH 7.2 was taken as the dissolution medium at 37±0.5ºC and 50rpm. 5ml of the sample was taken from the dissolution apparatus at predetermined time intervals for 24 hrs. The samples were replaced with the same quantity of medium. Absorbance of these solutions was measured at 222nm using UV Spectrophotometer. The concentration of the drug released at different time interval was determined from standard graph. From this cumulative % drug release was calculated and this was plotted against function of time to find out the pattern of drug release. The rates of the drug released were determined.

8. Drug Release Kinetics

Drug release kinetics was performed using model dependent method in which the dissolution profile of each formulation has been subjected various kinetics like zero order, first order, Higuchi's and korsmeyer-Peppas model.[44,45,46]

The data obtained from in vitro drug release studies were plotted in various kinetic models; as mentioned below zero order (Equation 1) as cumulative amount of drug released vs time, first order (Equation 2) as log as cumulative percentage of drug remaining vs time, and Higuchi's model (Equation 3)as cumulative percentage of drug released vs square root of time.

$$\mathbf{Q_t = Q_0 + k_0 t} \qquad \text{(Equation 1)}$$

Where Q_t is the amount of drug dissolved in time t,Q_0 is the initial amount of drug in the solution and K_0 is the zero-order rate constant expressed in units of concentration/time and t is the time in hours. A graph of concentration vs time would yield a straight line with a slope equal to K_0 and intercept the origin of the axis.

$$\mathbf{LogC = logC_O - kt/2.303} \qquad \text{(Equation 2)}$$

Where C_0 is the initial concentration of drug is the first order constant, and t is the time.

$$\mathbf{Q_t = K_H t^{1/2}} \qquad \text{(Equation 3)}$$

Where K_H is the constant reflecting the design variables of the system and t is the time in hours. Hence drug release rate is proportional to the reciprocal of the square root of time. Drug release were plotted in korsmeyer equation (Equation 4) as log cumulative percentage of drug released vs log time, and the exponent n was calculated through the slope of the straight line.

$$\mathbf{M_t/M_\infty = Kt^n} \qquad \text{(Equation 4)}$$

Where M_t/M_∞ is the fractional solute release, t is the release time, K is a kinetic constant.

Table 11: Diffusion Exponent and Solute Release Mechanism

Diffusion exponent (n)	Overall solute diffusion mechanism
0.45	Fickian diffusion
0.45<n<0.89	Anomalous (non-Fickian) diffusion
0.89	Case-II transport
n>0.89	Super case-II transport

9. Stability studies

Stability study was carried out to observe the effect of temperature and relative humidity on selected formulation (F7), by keeping at 40±2ºC, in air tight high density polyethylene bottles for six months, at RH 75±5%. Physical evaluation was carried out in each month.[81]

Table 12: ICH guidelines for Stability study

Study	Storage condition	Time period
Long term	25ºC±2ºC/60%RH±5%RH	12month
Intermediate	30ºC±2ºC/65%RH±5%RH	6 month
Accelerated	40ºC±2ºC/75%RH±5%RH	6 month

RESULTS AND DISCUSSION

Preparation of Calibration curve for Ibuprofen

The calibration curve of Ibuprofen was drawn by measuring the absorbance of different concentrations in phosphate buffer pH 7.2 at 222nm. The calibration curve obtained is shown in Table 13 and figure 12.

Table 13: Calibration curve of Ibuprofen

SI.No.	Concentration(µg/ml)	Absorbance(222nm)
1.	0	0
2.	10	0.151
3.	20	0.351
4.	30	0.521
5.	40	0.713
6.	50	0.912

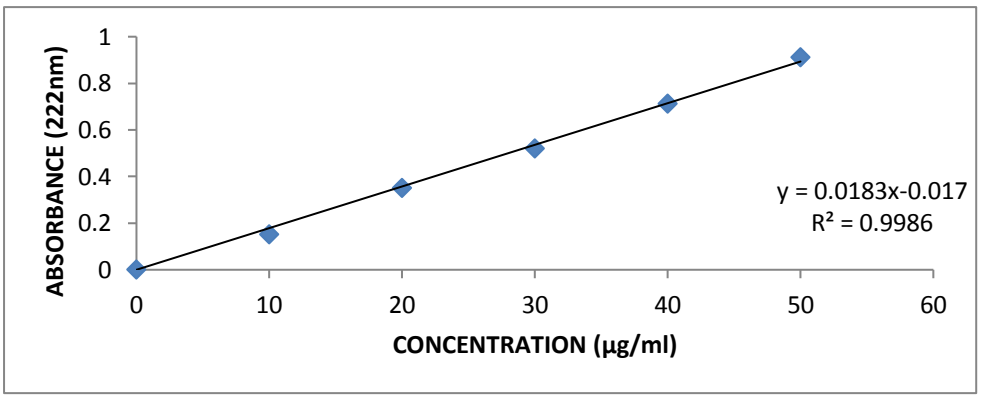


Figure 12: Calibration curve of ibuprofen

The calibration curves were linear and obeyed Beer-Lambert's law in the concentration range 10-50µg/ml. The correlation coefficient values were 0.9986 indicating excellent linearity of the data.

DRUG-EXCIPIENTS COMPATIBILITY STUDIES

Fourier Transform Infrared Studies

The FTIR Spectra of Ibuprofen in pure form and their physical mixture was observed, the result showed that there is no interaction between drug and polymers. From the FTIR spectral Figures 13to 21 Interpretations the following result was obtained. The FTIR of Ibuprofen and combinations of polymers shows intense band in the table 14 to 22 as follows.

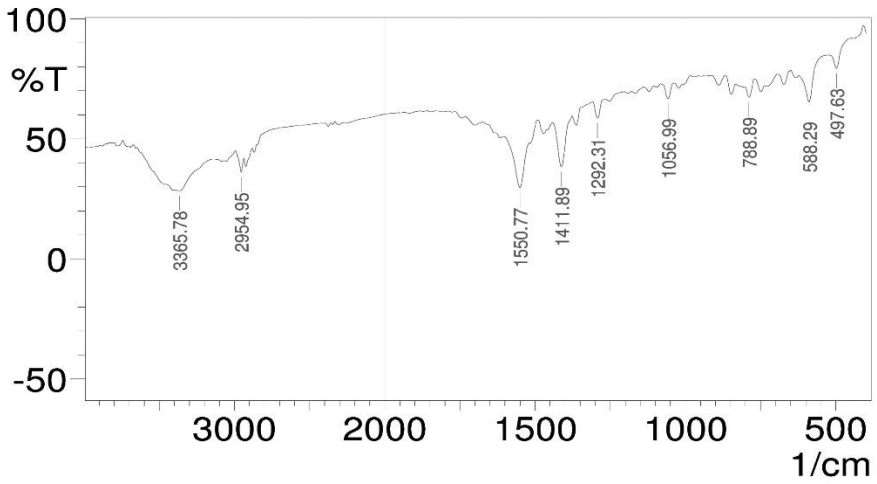


Figure 13: FTIR Spectrum of Ibuprofen

Table 14: Interpretation of Ibuprofen

Wave number cm^{-1}	Probable functional group
788.89	C-H bending (aro)
1411.89	C=C stretching(aro)
1550.7	C=O stretching (acid)
2954.95	C-H stretching (alkane)
3365.78	O-H stretching

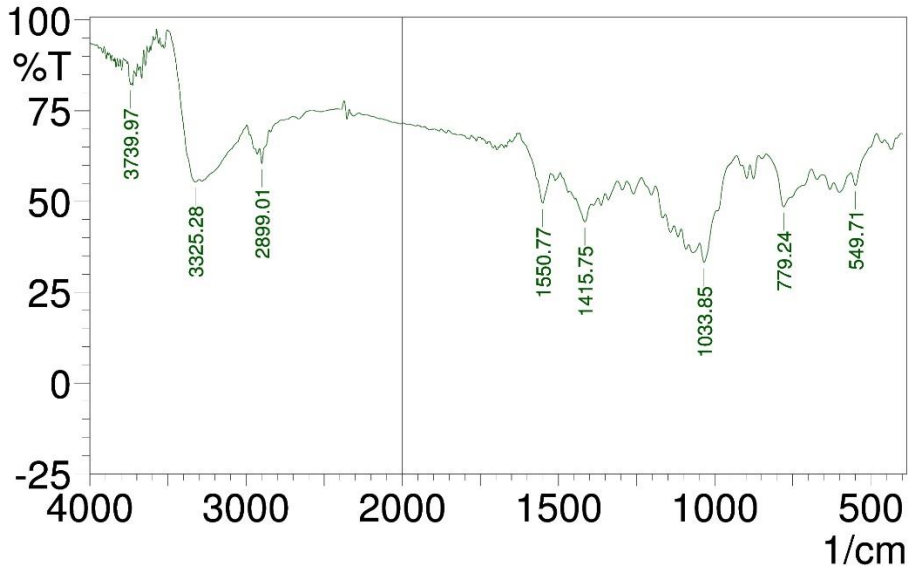


Figure 14: FTIR Spectrum of Ibuprofen+ Lactose monohydrate

Table 15: Interpretation of Ibuprofen+ Lactose monohydrate

Wave number cm^{-1}	Probable functional group
779.24	C-H bending (aro)
1415.7	C=C stretching(aro)
1550.77	C=O stretching (acid)
2899.01	C-H stretching (alkane)
3325.28	O-H stretching

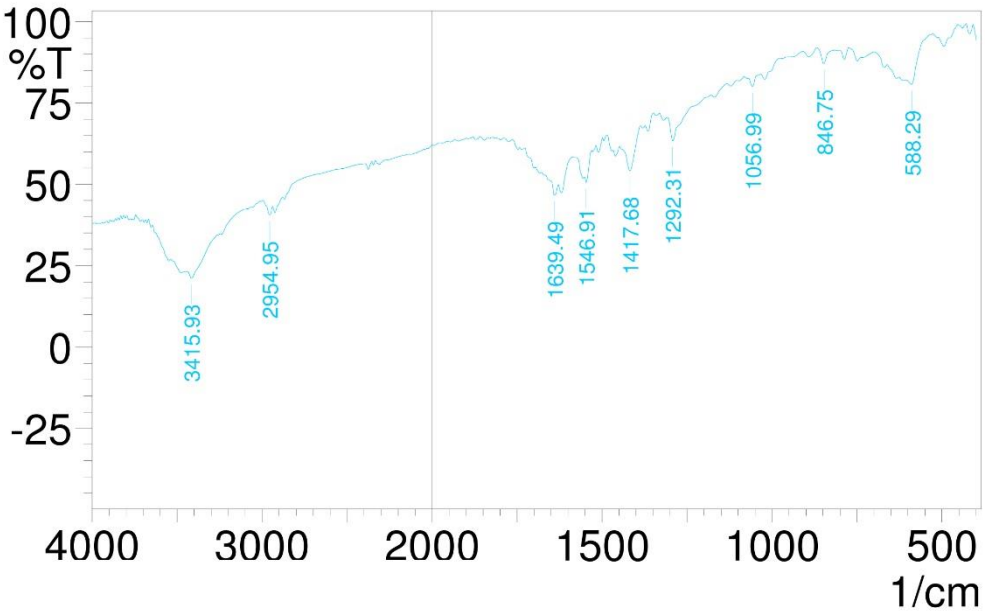


Figure 15:FTIR Spectrum of Ibuprofen+ Kollidon SR

Table 16: Interpretation of Ibuprofen+ Kollidon SR

Wave number cm^{-1}	Probable functional group
846.75	C-H bending (aro)
1417.68	C=C stretching(aro)
1639.49	C=O stretching (acid)
2954.95	C-H stretching (alkane)
3415.93	O-H stretching

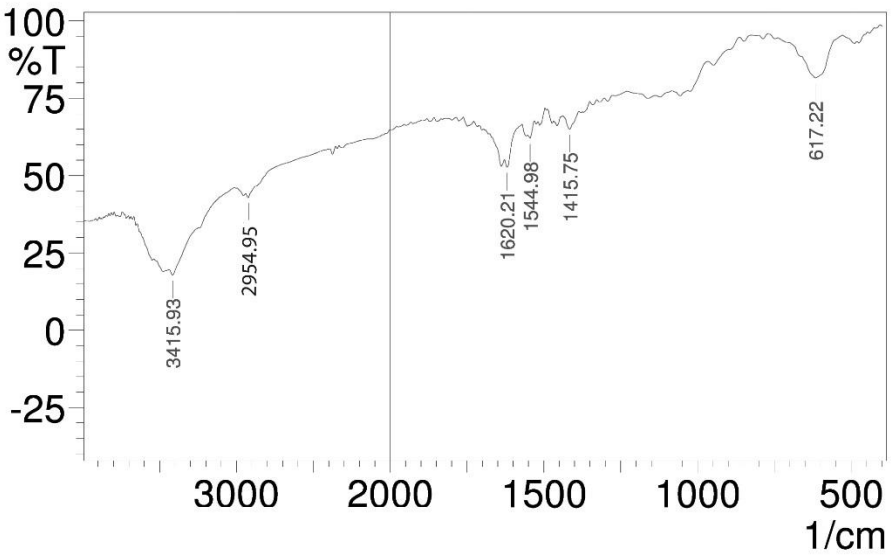


Figure 16: FTIR Spectrum of Ibuprofen+ HPMC K4 MCR

Table 17: Interpretation of Ibuprofen+ HPMC K4MCR

Wave number cm^{-1}	Probable functional group
617.22	C-H bending (aro)
1415.75	C=C stretching(aro)
1620.21	C=O stretching (acid)
2954.92	C-H stretching (alkane)
3415.93	O-H stretching

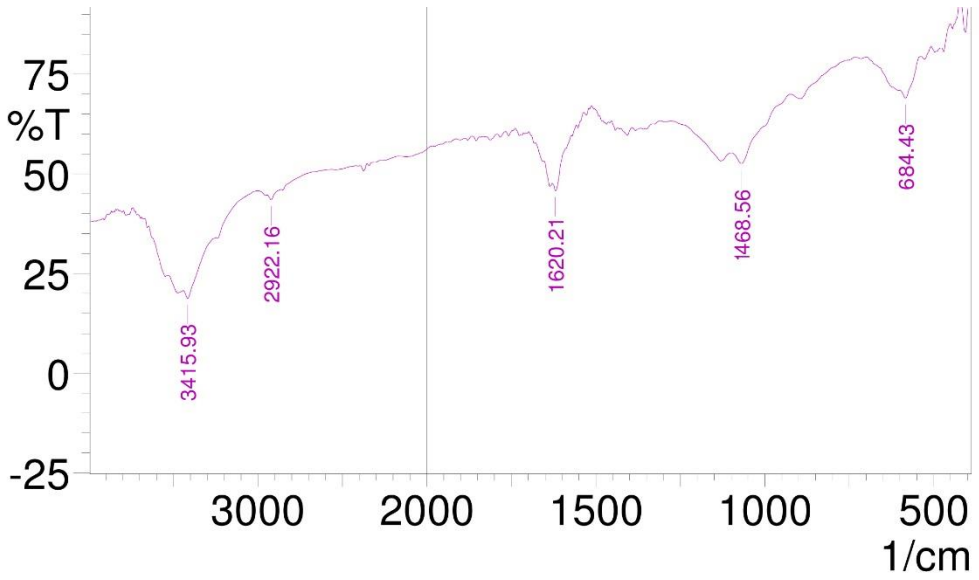


Figure 17: FTIR Spectrum of Ibuprofen+ HPMC K100 MCR

Table 18: I Interpretation of Ibuprofen+ HPMC K100MCR

Wave number cm^{-1}	Probable functional group
684.43	C-H bending (aro)
1468.56	C=C stretching(aro)
1620.21	C=O stretching (acid)
2922.16	C-H stretching (alkane)
3415.93	O-H stretching

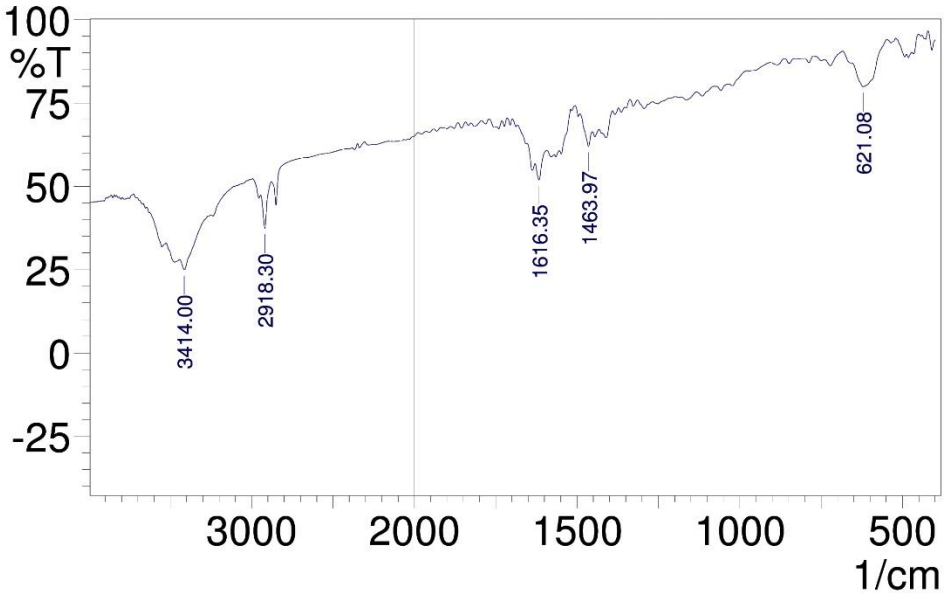


Figure 18:FTIR Spectrum of Ibuprofen+ Magnesium stearate

Table 19: Interpretation of Ibuprofen+ Magnesium stearate

Wave number cm^{-1}	Probable functional group
621.08	C-H bending (aro)
1463.97	C=C stretching(aro)
1616.35	C=O stretching (acid)
2918.30	C-H stretching (alkane)
3414.00	O-H stretching

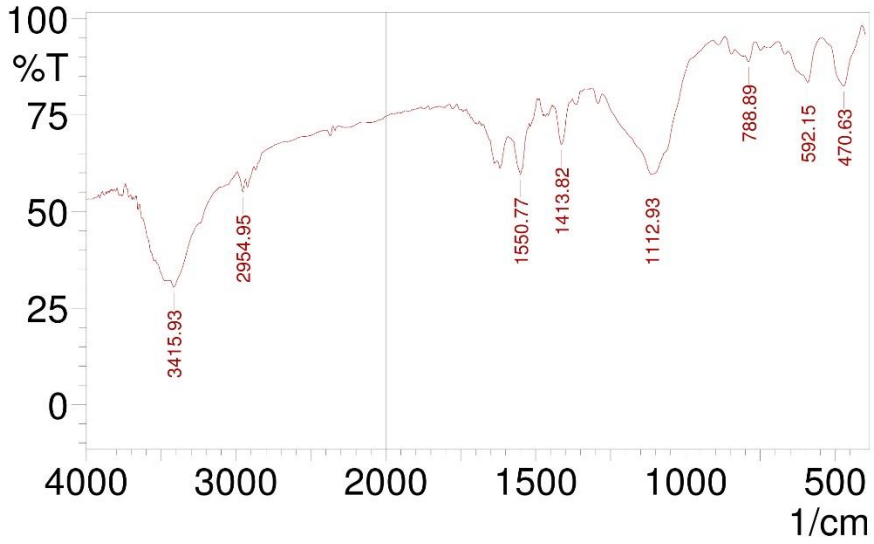


Figure 19:FTIR Spectrum of Ibuprofen+ Aerosil

Table 20: Interpretation of Ibuprofen+ Aerosil

Wave number cm^{-1}	Probable functional group
788.89	C-H bending (aro)
1413.82	C=C stretching(aro)
1550.77	C=O stretching (acid)
2954.95	C-H stretching (alkane)
3415.93	O-H stretching

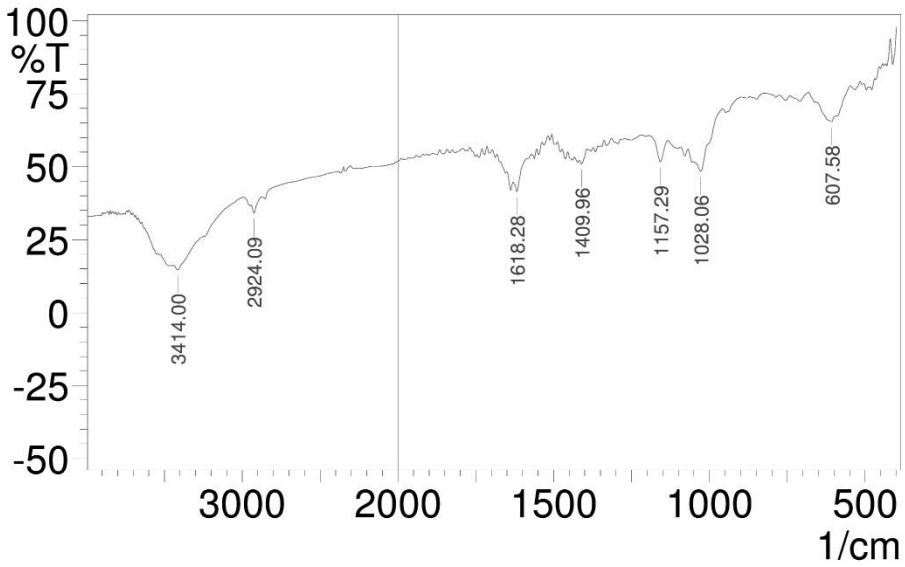


Figure 20: FTIR Spectrum of Ibuprofen+ Beta cyclodextrin Solid Dispersion

Table 21: Interpretation of Ibuprofen+ Beta cyclodextrin Solid dispersion

Wave number cm^{-1}	Probable functional group
607.58	C-H bending (aro)
1409.96	C=C stretching(aro)
1618.28	C=O stretching (acid)
2924.09	C-H stretching (alkane)
3414.00	O-H stretching

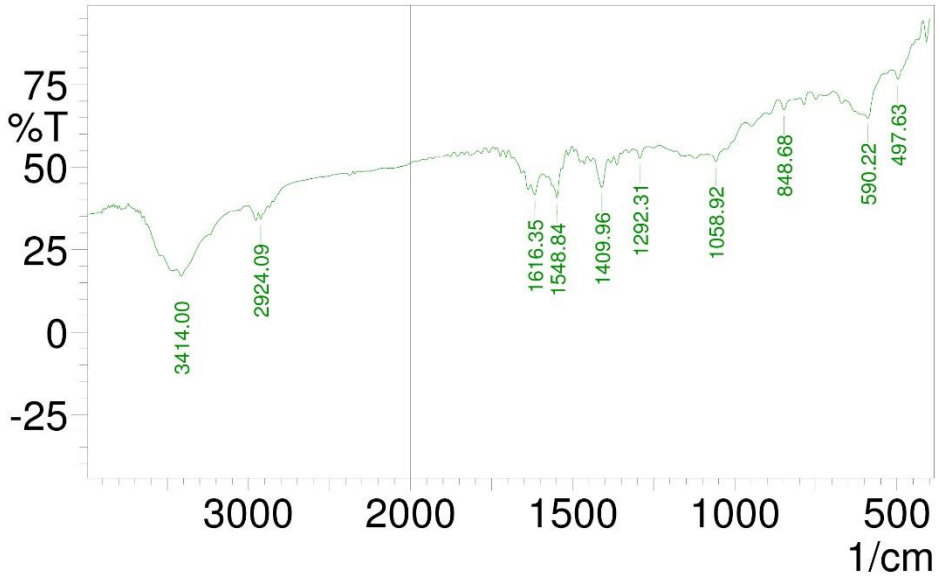


Figure 21: FTIR Spectrum of Ibuprofen tablet

Table 22: Interpretation of Ibuprofen tablet

Wave number cm^{-1}	Probable functional group
848.68	C-H bending (aro)
1409.96	C=C stretching(aro)
1616.35	C=O stretching (acid)
2924.09	C-H stretching (alkane)
3414	O-H stretching

Differential Scanning Calorimetry (DSC)

The compatibility and interactions between drugs and polymers were checked using DSC results obtained were shown in figure 22 to 23.

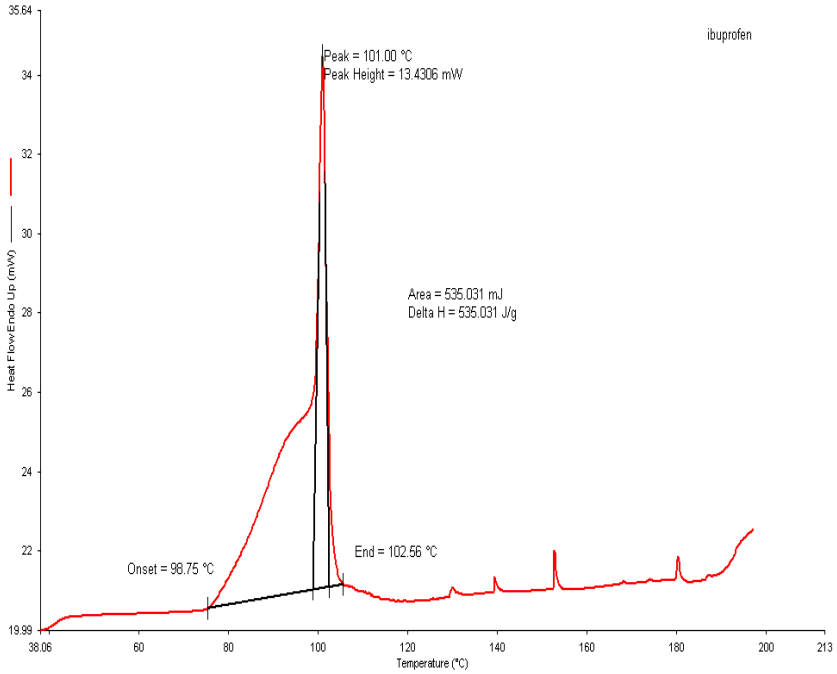


Figure 22: Differential Scanning Calorimetry of Ibuprofen

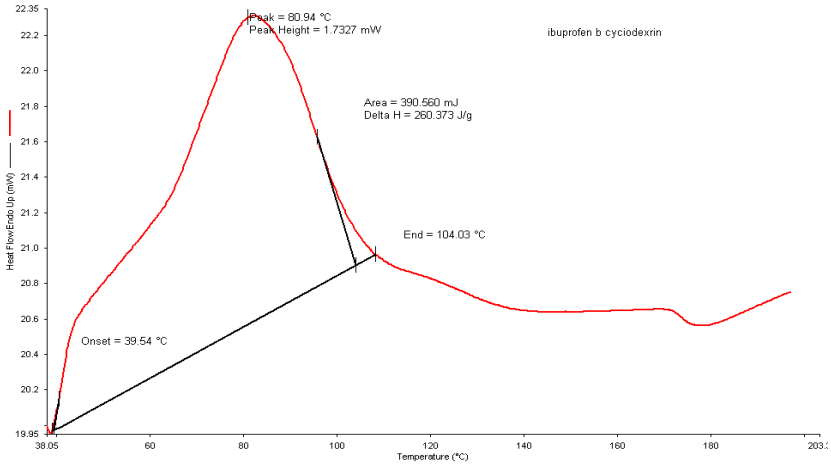


Figure 23: Differential Scanning Calorimetry of Ibuprofen + β-Cyclodextrin Solid dispersion

The DSC thermogram of pure Ibuprofen showed a sharp endothermic peak at 100.00ºC which corresponds to its melting point. The DSC thermogram of Ibuprofen-β-Cyclodextrin(1:3) solid dispersion prepared by a solvent evaporation method ($SD\beta_3$) showed endothermic peak at temperature 80.94ºC with some changes in the characteristics of the peaks. It showed that no possible interaction took place between the drug and carriers.

Evaluation of Ibuprofen solid dispersions and physical mixtures

Evaluation of drug content

The drug content of each solid dispersion batch and physical mixture were determined by UV-spectrophotometry measured at 222nm.

Table 23: Drug content of evaluation of solid dispersion containing Drug and Carriers for various formulations

Batch code	% Drug content ±S.D
PM_1	95±0.42
PM_2	93±0.16
$S.D\beta_1$	90±0.18
$S.D\beta_2$	95±0.78
$S.D\beta_3$	99±0.83
$S.DP_1$	91±0.74
$S.DP_2$	92±0.84
$S.DP_3$	93±0.74

***In vitro* drug release study of solid dispersion containing Drug and carriers for various formulations**

Table 24: *In vitro* drug release study of solid dispersion containing Drug and carriers for various formulations

Time (min)	Cumulative Percentage of Drug Released ± S.D							
	P.M$_1$	**P.M$_2$**	**S.Dβ$_1$**	**S.D β$_2$**	**S.D β$_3$**	**S.D P$_1$**	**S.D P$_2$**	**S.D P$_3$**
0	0	0	0	0	0	0	0	0
5	10±0.27	11±0.26	10±0.11	13±0.15	12±0.13	10±0.16	10±0.11	12±0.12
10	23±0.32	20±0.34	12±0.12	22±0.37	20±0.32	23±0.22	20±0.54	24±0.45
15	45±0.33	34±0.24	16±0.24	30±0.22	23±0.63	31±0.34	28±0.22	29±0.27
20	50±0.24	46±0.32	20±0.14	40±0.68	30±0.24	52±0.18	35±0.33	32±0.36
25	53±0.67	53±0.63	27±0.23	52±0.35	36±0.16	70±0.16	46±0.56	38±0.24
30	59±0.63	64±0.34	33±0.88	60±0.54	48±0.34	74±0.14	50±0.38	46±0.28
35	64±0.62	76±0.48	38±0.54	67±0.18	52±0.25	79±0.18	63±0.13	56±0.44
40	69±0.54	80±0.26	42±0.82	70±0.17	67±0.23	84±0.20	68±0.26	64±0.83
45	73±0.36	83±0.36	50±0.24	72±0.19	78±0.26	88±0.23	74±0.16	73±0.56
50	79±0.42	88±0.24	63±0.56	80±0.17	80±0.48	90±0.18	84±0.22	86±0.38
55	82±0.64	90±0.38	72±0.58	86±0.19	92±0.16	93±0.27	89±0.43	90±0.22
60	86±0.62	92±0.42	80±0.88	90±0.38	98±0.32	96±0.30	93±0.26	95±0.32

Each value was an average of six determinations (n=6) ± S.D (Standard Deviation)

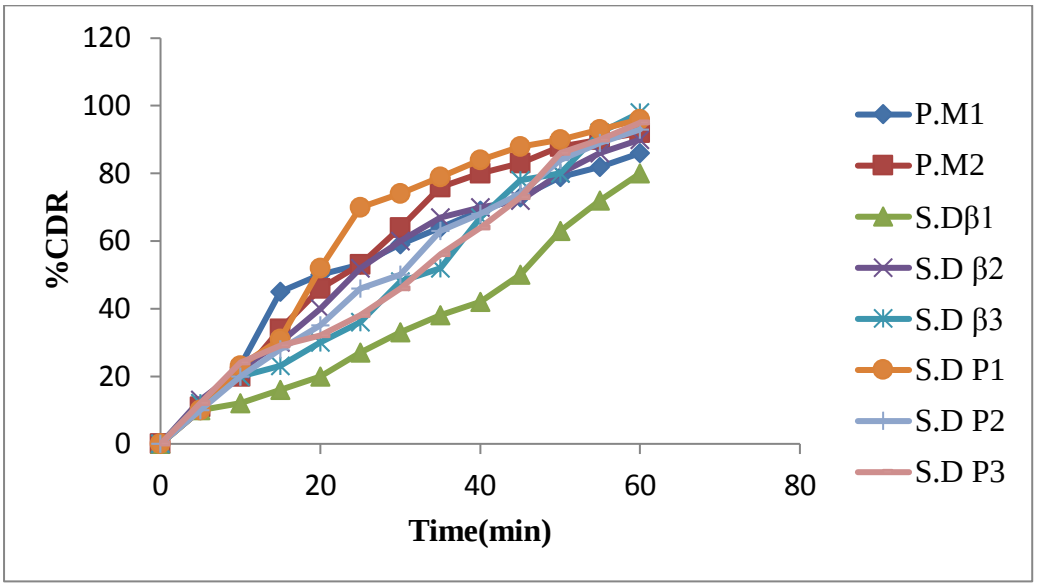


Figure 24: *In vitro* drug release study of solid dispersion containing Drug and Carrier for various formulations

The solid dispersion of S.D β_3 batch showed maximum drug content [99±0.83] and drug release [98%] within 60 minutes, among all the formulations and this ratio can be used to enhance the solubility and dissolution rate of poorly water soluble drug Ibuprofen. It was observed that the drug release was increased with increasing the quantity of β-cyclodextrin.

Evaluation of Pre-compression of Ibuprofen SR granules

Table 25: Pre-Compression parameters of Ibuprofen Trial batch **F1IB-F10IB**

Formulation Code	Angle of Repose(Ɵ)	Bulk Density(gm/cm^3)	Tapped Density(gm/cm^3)	Carr's index(%)	Hausner's ratio
F1IB	25º.16'±0.14	0.572±0.05	0.640±0.07	10.62±0.28	1.11±0.07
F2IB	25º.73'±0.57	0.562±0.04	0.634±0.08	10.36±0.32	1.10±0.02
F3IB	25º.88'±0.06	0.570±0.02	0.627±0.04	11.50±0.56	1.13±0.04
F4IB	25º.08'±0.12	0.582±0.03	0.624±0.02	11.24±0.45	1.11±0.03
F5IB	25º.95'±0.36	0.552±0.01	0.654±0.04	11.05±0.36	1.12±0.25
F6IB	25º.02'±0.54	0.554±.0.03	0.642±0.02	10.84±0.45	1.13±0.23
F7IB	25º.44'±0.58	0.556±0.02	0.613±0.06	11.60±0.28	1.12±0.08
F8IB	25º.56'±0.76	0.558±0.04	0.645±0.08	10.56±0.46	1.10±0.04
F9IB	25º.01'±0.19	0.565±0.08	0.653±0.02	9.75±0.34	1.11±0.28
F10IB	24º.96'±0.18	0.577±0.04	0.628±0.06	9.92±0.27	1.13±0.24

All values are mean ± S.D n=3

The angle of repose was found to be ranging from **24º96'±0.18 to 25º95'±0.36** for all formulations.

The Bulk density and Tapped density of the prepared blend ranged from **0.552±0.01 to 0.582±0.03 gm/cm^3** and **0.613±0.06 to 0.654±0.04 gm/cm^3** respectively.

The Compressibility index was found to ranging from **9.75±0.34 to 11.60±0.28%**

The Hausner's ratio ranged from **1.10±0.02 to 1.13±0.24**. The granules are having good flow property.

From the results of precompression evaluation all the formulations having good flowing property and the results are within the pharmacopoeial limit.

Evaluation of Post compression parameters of Ibuprofen Sustained release tablets

Table 26: Post-Compression parameters of Ibuprofen Trial batch **F1IB – F10IB**

Formulations	Thickness (mm)	Diameter (mm)	Hardness (kg/cm^2)	Friability (%)	Weight variation(mg)	Drug Content(%)
F1IB	4.04±0.02	12±0	4.43±0.58	0.85±0.10	600.3±1.69	96.46±1.05
F2IB	4.04±0.01	12±0	4.27±0.56	0.84±0.11	600.1±1.68	95.22±1.04
F3IB	4.06±0.02	12±0	4.42±0.54	0.85±0.12	600.4±1.64	93.13±1.46
F4IB	4.08±0.01	12±0	4.44±0.78	0.87±0.11	600.0±1.22	94.24±1.22
F5IB	4.09±0.52	12±0	4.45±0.28	0.86±0.10	600.2±2.14	92.12±0.90
F6IB	4.07±0.54	12±0	4.48±0.31	0.88±0.11	600.4±1.26	98.14±0.12
F7IB	4.09±0.02	12±0	4.49±0.32	0.85±0.10	600.0±2.65	99.80±0.48
F8IB	4.08±0.01	12±0	4.42±0.30	0.84±0.13	600.2±1.43	95.64±0.42
F9IB	4.05±0.03	12±0	4.40±0.31	0.84±0.12	600.4±1.63	92.64±0.34
F10IB	4.06±0.01	12±0	4.34±0.35	0.83±0.14	600.3±1.47	90.29±0.52

All values are mean ±S.D n=3

The result of post compression parameters of all formulations are shown in table 26.

The thickness was ranged between **4.04±0.01mm to 4.09±0.52mm**, indicating the uniformity in thickness.

Diameter for all the formulation was **12±0mm** showed there was no significance difference.

The hardness of all formulation in ranges from **4.27±0.56 to 4.49±0.32 kg/cm^2**.

The friability was less than 1% indicating good integrity of the tablet.

The weight variation of all formulations range from **600.0±1.22 to 600.0±2.65 mg**. The values are within the acceptable range of pharmacopoeial specification.

The drug content was in the range of **90.29±0.52 to 99.80±0.48%** indicated good content uniformity.

In-vitro Drug Release of Ibuprofen SR Tablets

Table 27: *In-vitro* Drug Release profile data of various formulations of Ibuprofen sustained release Tablets

Time in Hours	Cumulative Percentage of Drug Released ±S.D									
	F1IB	**F2IB**	**F3IB**	**F4IB**	**F5IB**	**F6IB**	**F7IB**	**F8IB**	**F9IB**	**F10IB**
1	3.86 ±1.00	4.03 ±1.17	4.02 ±0.95	3.46 ±1.00	4.07 ±0.95	4.05 ±0.93	**2.66 ±0.12**	2.38 ±0.14	2.50 ±0.50	2.26 ±0.34
2	12.04 ±0.77	7.36 ±1.12	11.25 ±0.68	12.68 ±0.76	7.66 ±1.10	9.64 ±1.08	**4.09 ±0.34**	8.05 ±0.96	3.74 ±0.14	4.56 ±0.23
3	19.95 ±0.20	12.81 ±0.07	22.98 ±1.65	20.95 ±0.21	11.81 ±0.07	13.81 ±0.86	**11.72 ±0.02**	10.56 ±0.54	11.70 ±0.51	10.45 ±0.66
4	27.67 ±1.26	14.09 ±0.56	27.47 ±3.74	26.67 ±1.20	13.10 ±0.07	21.96 ±1.64	**16.34 ±0.92**	14.68 ±0.68	16.53 ±0.38	15.46 ±0.24
5	30.33 ±0.17	19.46 ±0.27	35.20 ±0.06	29.32 ±1.28	18.49 ±0.27	25.47 ±3.46	**18.62 ±0.21**	16.68 ±0.42	20.36 ±0.08	18.78 ±0.78
6	36.90 ±1.97	29.64 ±0.41	38.96 ±0.72	30.43 ±2.28	29.66 ±0.41	32.20 ±0.74	**24.32 ±0.30**	22.28 ±1.75	25.11 ±0.24	20.24 ±0.09
7	43.49 ±0.31	32.26 ±2.19	42.80 ±0.47	35.20 ±0.07	32.28 ±2.19	36.98 ±0.72	**36.34 ±0.11**	25.10 ±0.24	28.76 ±0.48	22.78 ±1.64
8	44.47 ±1.24	36.20 ±1.06	44.43 ±1.24	38.97 ±0.73	36.20 ±1.04	38.97 ±0.73	**44.23 ±0.46**	28.76 ±0.44	35.60 ±1.41	26.44 ±3.74
9	49.13 ±0.69	38.71 ±0.17	49.13 ±0.69	42.85 ±0.43	38.70 ±0.16	40.86 ±0.47	**50.09 ±0.62**	34.20 ±1.43	37.84 ±0.04	35.20 ±0.06
10	51.45 ±1.24	41.94 ±2.73	51.45 ±1.22	44.47 ±1.22	41.92 ±2.72	42.84 ±0.46	**54.90 ±0.17**	46.38 ±0.56	40.52 ±0.78	38.97 ±0.73
11	54.22 ±0.43	44.53 ±1.15	62.40 ±0.64	48.24 ±0.50	44.55 ±1.15	44.47 ±1.24	**58.47 ±0.14**	51.45 ±1.26	41.45 ±0.46	42.86 ±0.47
12	62.44 ±0.67	48.44 ±0.51	66.78 ±0.76	51.98 ±1.24	47.49 ±0.51	49.13 ±0.69	**60.89 ±0.20**	58.61 ±0.43	44.82 ±1.10	46.14 ±0.68
13	64.91 ±0.84	50.79 ±0.14	70.24 ±0.09	63.43 ±0.73	50.76 ±0.12	52.46 ±1.26	**70.25 ±0.80**	62.48 ±0.64	49.90 ±0.10	50.44 ±1.26
14	65.36 ±0.44	55.74 ±1.44	74.85 ±0.58	65.74 ±0.46	55.75 ±1.44	62.44 ±0.67	**74.33 ±0.06**	66.80 ±0.78	50.34 ±0.42	58.78 ±0.16
15	70.28 ±0.09	58.40 ±0.42	80.86 ±0.59	68.34 ±0.34	58.38 ±0.42	68.80 ±0.74	**78.74 ±0.24**	72.85 ±0.58	53.64 ±0.86	62.44 ±0.68
16	74.85 ±0.58	60.91 ±0.43	82.23 ±1.84	72.66 ±0.58	60.73 ±0.42	70.28 ±0.09	**81.24 ±0.46**	78.44 ±0.06	58.82 ±0.13	66.80 ±0.76
17	76.59 ±1.17	65.54 ±0.46	83.62 ±0.64	77.86 ±1.16	65.54 ±0.48	74.82 ±0.56	**88.94 ±0.16**	82.64 ±1.82	60.18 ±0.41	71.46 ±0.09
18	78.20 ±0.04	69.74 ±0.12	87.72 ±0.40	81.12 ±0.49	69.76 ±0.14	80.05 ±0.58	**92.97 ±0.26**	84.42 ±0.68	65.49 ±0.65	74.85 ±0.58
19	80.06 ±0.59	73.25 ±0.64	89.92 ±0.56	83.68 ±0.66	72.25 ±0.62	81.27 ±1.84	**93.01 ±1.00**	88.24 ±0.54	69.20 ±0.64	78.86 ±0.57
20	81.10 ±0.48	77.42 ±0.40	92.26 ±0.10	86.89 ±0.56	76.24 ±0.40	83.63 ±0.68	**93.19 ±0.86**	90.26 ±0.10	77.25 ±0.25	82.63 ±0.64
21	82.27 ±1.86	79.22 ±0.41	93.48 ±0.58	88.46 ±0.64	78.24 ±0.41	87.74 ±0.40	**94.10 ±0.97**	92.36 ±0.10	80.16 ±0.52	86.16 ±0.52
22	83.63 ±0.65	81.92 ±0.70	94.10 ±0.56	90.64 ±0.88	81.92 ±0.71	89.96 ±0.56	**94.97 ±0.74**	93.34 ±0.54	83.23 ±0.43	90.26 ±0.12
23	87.74 ±0.40	85.37 ±1.54	95.78 ±0.53	92.67 ±0.10	85.37 ±1.54	92.26 ±0.12	**95.99 ±0.18**	95.46 ±0.65	83.36 ±0.27	93.49 ±0.56
24	89.98 ±0.56	85.81 ±0.73	96.32 ±0.86	94.48 ±0.66	86.81 ±0.73	93.49 ±0.58	**99.41 ±0.16**	96.91 ±0.28	84.76 ±0.65	95.68 ±0.76

Each value was an average of six determinations (n=6)± S.D (standard Deviation)

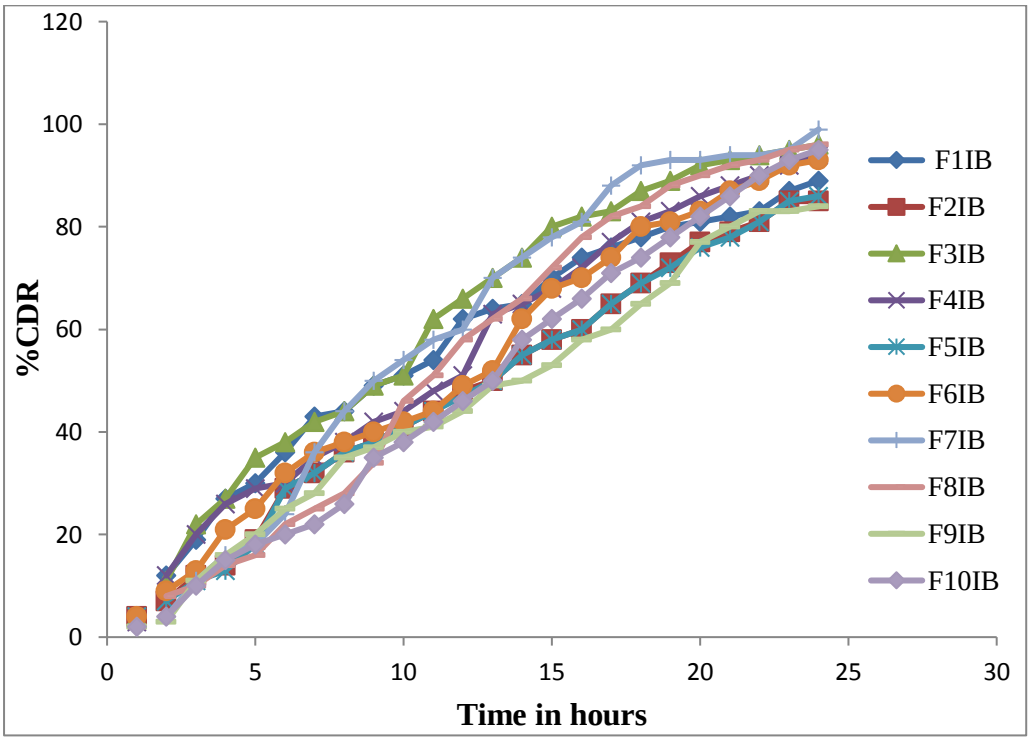


Figure 25: *In vitro* cumulative (%) Drug Release profile data of various formulations of Ibuprofen Sustained release tablets

The *In vitro* cumulative (%) drug release profile data of various formulations of Ibuprofen Sustained release tablets are shown in **Table 27** and **Figure 25**. Based on the results Formulation(F7IB) only succeeded to allow a sustained release of drug. At the end of 24hrs highest drug release 99.41% and so it was considered as the optimized batch.

Comparison of selected formulations with marketed formulations

Table 28: *In vitro* Dissolution profile of Marketed Ibuprofen SR formulations and Sustained release of Ibuprofen formulation (F7IB)

Time (Hrs)	%CDR ±S.D	
	Marketed formulation Ibuprofen	F7IB
0	0	0
2	4.86±0.33	11.72±0.34
4	13.44±0.58	18.62±0.92
6	58.86±0.43	24.53±0.30
8	69.62±0.24	44.09±0.46
10	80.16±0.48	64.32±0.17
12	86.34±0.62	85.30±0.20
14	89.69±0.41	88.17±0.06
16	91.46±0.38	91.09±0.46
18	94.57±0.54	92.97±0.26
20	95.34±0.82	93.19±0.86
22	97.23±0.74	94.97±0.74
24	99.86±0.66	99.41±0.16

Each value was an average of six determinations (n=6) ± S.D (standard Deviation)

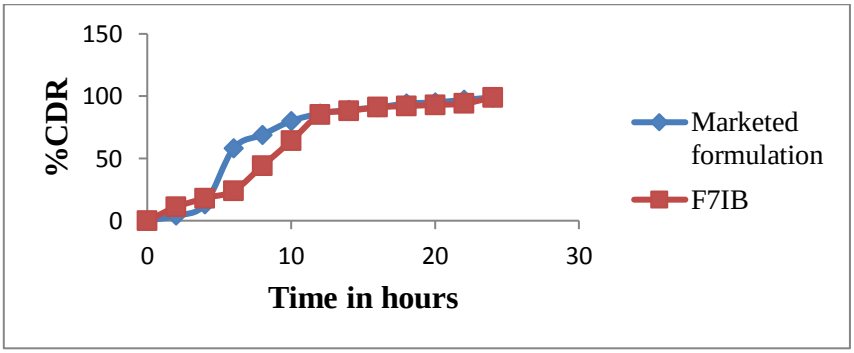


Figure 26: *In vitro* Dissolution profile of marketed Ibuprofen Sustained Release formulation and Sustained Release of Ibuprofen formulation (F7IB)

In marketed formulation 99.86% of release was observed within 24hrs and sustained release of Ibuprofen formulation (F7IB) 99.41% of release was observed within 24hrs.

Dissolution Kinetics

Dissolution kinetics for Formulation 7 (F7IB)

The dissolution profiles of formulation F7 was subjected to various kinetic studies and are depicted in the following figure 27 to 30.

Table 29: Drug release kinetic models for Ibuprofen sustained release tablets of Formulation(F7IB)

Log T	T	%DR	REMAIN DR	% LOG CUMU DR	SQRT T	LOG % DR
0.0	0	0.00	100	2	0.00	0.00
0.3	2	4.09	95.91	1.98	1.41	0.61
0.6	4	16.34	83.66	1.92	2.00	1.21
0.8	6	24.32	75.68	1.88	2.45	1.39
0.9	8	44.23	55.77	1.75	2.83	1.65
1.0	10	54.90	45.1	1.65	3.16	1.74
1.1	12	60.89	39.11	1.59	3.46	1.78
1.1	14	74.33	25.67	1.41	3.74	1.87
1.2	16	81.24	18.76	1.27	4.00	1.91
1.3	18	92.97	7.03	0.85	4.24	1.97
1.3	20	93.19	6.81	0.83	4.47	1.97
1.3	22	94.97	5.03	0.70	4.69	1.98
1.4	24	99.41	2.59	0.41	4.90	1.99

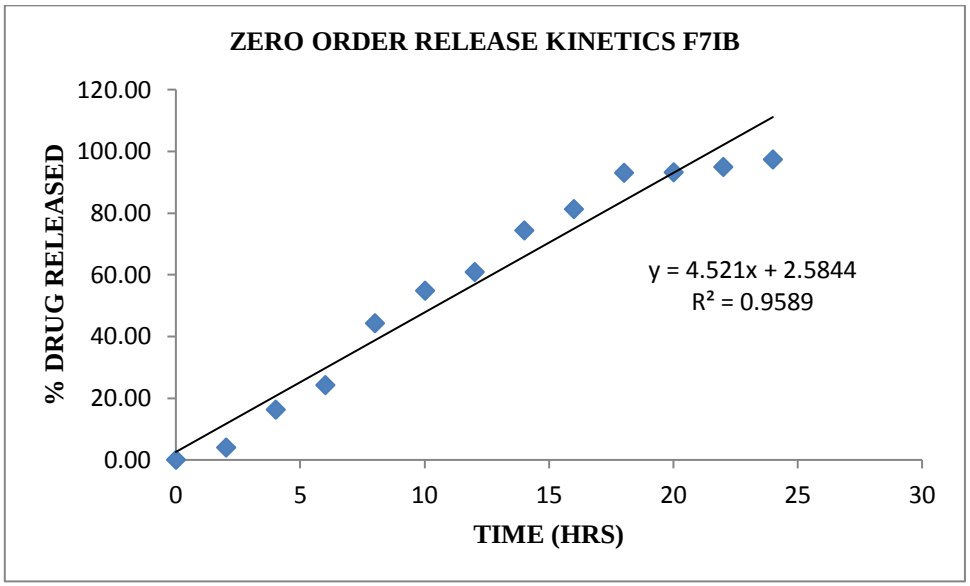


Figure 27: Zero order release kinetics F7IB

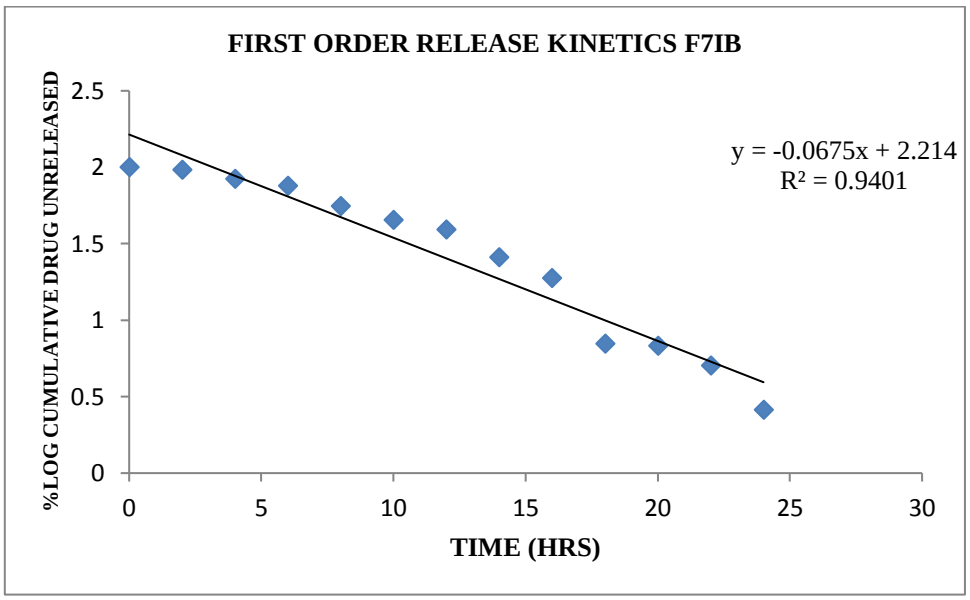


Figure 28: First order release kinetics F7IB

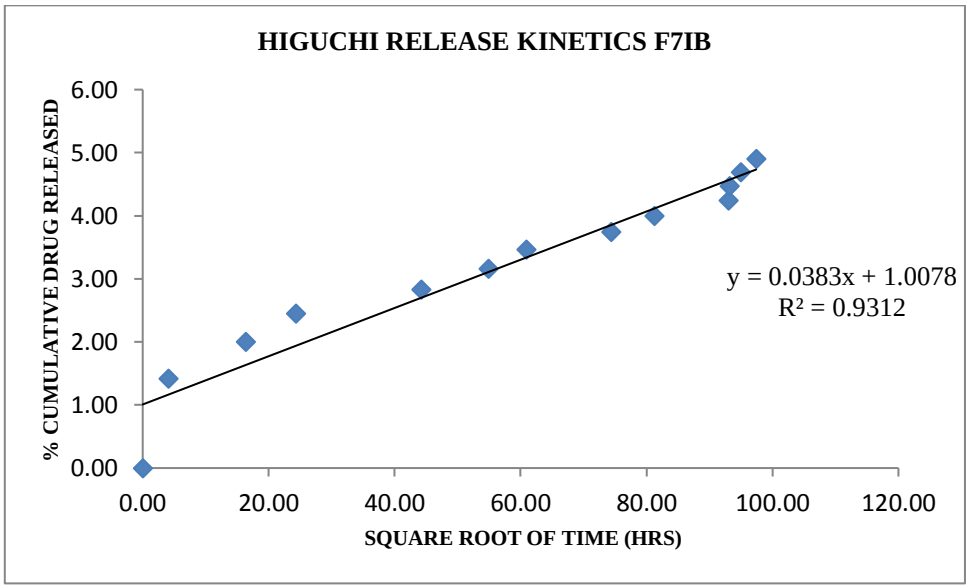


Figure 29: Higuchi release kinetics F7

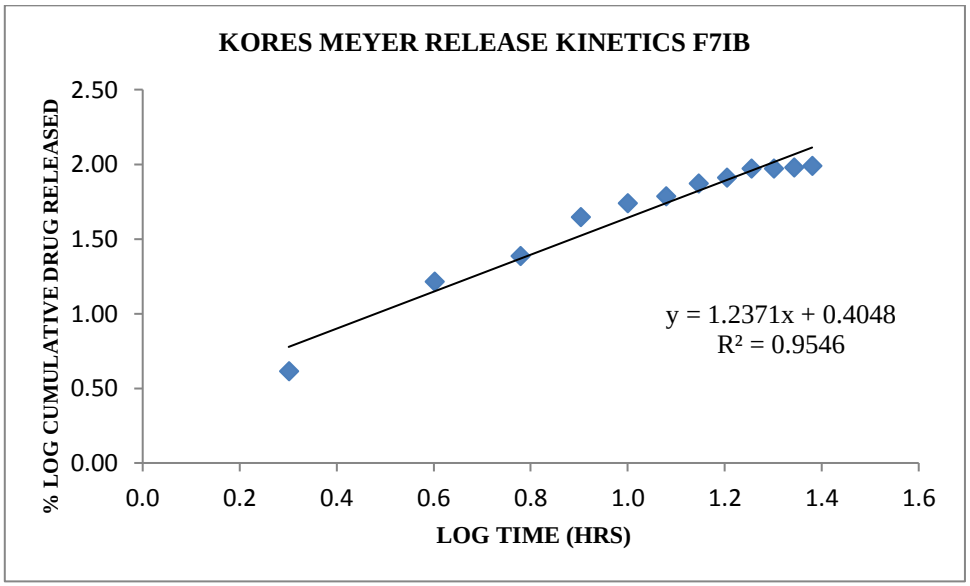


Figure 30: Korsmeyer release kinetics F7IB

Table 30: Release kinetics data optimized Ibuprofen Sustained release tablet(F7IB)

Formulation	Model	R^2	Slope	K
F7IB	Zero Order	0.9589	4.521	2.5844
	First Order	0.9401	0.0675	2.214
	Higuchi Model	0.9312	0.0383	1.0078
	Korsmeyer Model	0.9546	1.2371	0.4048

The *In vitro* release data of F7IB was fitted with various kinetics equations. From the table (30), it was shown that the regression coefficient [r^2=0.9589] value was more in Zero order and Korsmeyer model [r^2=0.9546].

The value of 'n' was found to be 0.4048 which indicates that the drug release follows Fickian diffusion.

STABILITY STUDY

After storage the formulation was analysed for various parameters, results are showed in Table 31.

Table 31: Stability study of best formulation F7IB

Characteristic	Initial	1st Month	2st Month	3st Month	6st Month
Appearance	White	No change	No change	No change	No change
Texture	Smooth	Smooth	Smooth	Smooth	Smooth
Drug content(%)	99.80±0.48	99.5±0.45	99.04±0.62	98.89±0.45	98.79±0.54
%of Drug release	97.41 ±0.16	97.23±0.34	96.45±0.22	96.24±0.43	96.01±0.42

All the values are expressed as mean ±SD, n=3

From the table 31, there was no visible changes in the appearance of the formulation [F7IB], and the drug content and dissolution profile of the optimized formulation was related to the initial reference.

SUMMARY AND CONCLUSION

The objective of the present study was developed as sustained release tablets of Ibuprofen by solid dispersion technique. The results of FTIR study and DSC study confirmed that there is no chemical interaction or no incompatibility between the drug and excipients. The solid dispersion technique would be an effective approach for increasing the solubility and increasing dissolution behaviour of poorly water soluble drug. The granules were evaluated for precompression parameters like Bulk density, Tapped density, Angle of repose, Carr's index, Hausner's ratio.

Ten formulations were fabricated using with suitable rate controlling polymers like HPMCK4MCR, HPMCK100MCR. The compressed tablets were evaluated for post compressive parameters like Weight variation, Friability, Hardness, Drug content, was within the Pharmacopoeial limit.

The *in vitro* dissolution study was performed for various formulations and marketed formulation. Based on the results F7IB was shown highest drug release 99.41% within 24hrs. Various formulations were subjected to various model dependent kinetics like Zero order, First order, Higuchi, Korsmeyer-peppas release kinetics. The release profile exhibiting maximum r^2 value was found to obey that Fickian diffusion kinetics. It was observed F7IB was found to be Zero order release kinetics.

Stability study was conducted as per ICH guidelines and the results showed that there is no physical or chemical change.

It may be concluded that the sustained release tablets of Ibuprofen by solid dispersion technique may reduce the dosing frequency and improve the patient compliance.

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